OFFICE OF SCIENCE AND TECHNOLOGY

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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 Office of Science and Technology (OST) is the laboratory of the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration.

OST supports the scientific basis for the Agency's regulatory policies through the development of independent laboratory information for regulatory and other public health activities of CDRH. OST accomplishes this mission by managing, developing, and supporting standards used for regulatory assessments; performing laboratory evaluations and analyses in support of CDRH premarket and postmarket activities; developing data needed for current and future regulatory problems; and performing research, anticipating the impact of technology on the safety, effectiveness, and use of regulated products.

Specifically, OST develops and conducts research and testing programs in the areas of physical, life, and engineering sciences related to the human health effects of radiation and medical device technologies. OST develops specific scientific expertise for CDRH decision-making and analyses for health-risk assessments. The Office develops new or improved measurement methods, techniques, instruments, and analytical procedures for evaluating product performance and reliability. OST also provides innovative solutions to public health problems by developing generic techniques to enhance product safety and effectiveness. The Office prepares CDRH with the targeted science needed to ask the right questions early. The laboratory activities of the Office have four major focus areas: characterization of the constituents or components of products; measurement of product performance; bioeffects which derive from human exposure to radiation or medical devices; and radiation metrology in support of Agency regulation of radiation-emitting products.

The OST Annual Report updates information about OST's organization, staffing, and intramural science activities; provides a summary of our direct laboratory support for premarket review and compliance cases; and provides a bibliography of scientific publications, presentations, contracts, patents, and research seminars of the Office for fiscal year 2001. The report might also be viewed as a source of information regarding areas in which Cooperative Research and Development Agreements (CRADAs) can be initiated. OST welcomes comments on the programs described in this report. We hope you find this report useful and informative, and we invite your comments. For additional information, please contact us at 301.827.4777.

Donald E. Marlowe
Director

ARTIFICIAL ORGAN REPLACEMENTS AND ASSISTS

Advances in the development of artificial organs and organ assists will be driven by the continuing dearth of natural donor organs. The products in this category are among the most complex that the Center evaluates, and their public health significance is often profound. OST's projects are directed toward elucidating the underlying mechanisms by which these devices interact with the body so as to provide methods for addressing key issues of safety and effectiveness. These activities are targeted to identify key scientific questions early in the Total Product Life Cycle for new technologies, and to provide meaningful techniques to answer those questions.

OST's Division of Physical Sciences (DPS) has a number of issues under investigation related to the successful use of artificial organs and organ assists including 1) damage to blood induced by cardiovascular devices, 2) the safety and effectiveness of prosthetic heart valves, 3) the consistency in performance of cerebral spinal fluid shunts, 4) the optical quality of intraocular lens implants for refractive corrections of otherwise healthy eyes, and 5) issues related to neural stimulation. In each case, the goal is to develop information that will assist Center decision-making in the timely assessment either of manufacturer's submissions or of unforeseen problems following introduction into commerce.

Many of these projects are directly coupled into regulatory guidance and standards-setting activities. For example, the need for better designs fuels a steady stream of heart valve submissions to the Agency. The goal of the laboratory effort is to provide reliable, easily interpreted methods for evaluating new heart valve designs. DPS also has a long history of working with both national (ANSI) and international (ISO) standards groups to develop standards on refractive implants. Current laboratory work examines the performance of new intraocular lenses (IOLs) being developed for the correction of myopia and hyperopia. These phakic IOLs are implanted in otherwise healthy eyes and the natural crystalline lens is left intact. This new wave of phakic IOLs implanted in otherwise healthy eyes, addresses patients with severe corrections that are difficult to treat with spectacles, contact lenses or laser surgery. DPS' laboratory studies develop test methods and performance standards for assessing the optical quality of these new IOLs. Laboratory work on electrical stimulation has been used to help formulate

regulatory guidance for spinal cord stimulators, and to revise national standards for nerve stimulators. Additionally, this research serves as a basis for the pre-market review of a number of investigational sense-organ replacement devices, including cochlear and middle ear implants as well as artificial retinas.

Assessing Blood Trauma in Medical Devices

Key words: hemolysis, blood damage, medical devices

Prior to their use in patients, medical devices are evaluated for their potential to damage or activate blood elements by a battery of laboratory tests. One aspect of this *hemocompatibility* evaluation includes determining that both the materials used in the device and the device itself, when operated at its maximum conditions, do not cause excessive damage to red blood cells (i.e., hemolysis). In the past year OST scientists continued to standardize the assessment of chemically and mechanically induced blood trauma in medical devices.

OST worked with manufacturer testing laboratories to upgrade and evaluate the testing methodology in the document "Standard Practice for Assessment of Hemolytic Properties of Materials (ASTM F756)" for use in national and international standards. To test for chemically induced blood damage in this standard, medical device materials and their extracts are exposed separately to rabbit blood under static test conditions. Interlaboratory round-robin testing using positive and negative control materials and extracts showed consistent results within each laboratory. However, the more variable results between laboratories are being used to determine precision and bias for the test system.

OST scientists also joined researchers from the University of Pittsburgh Medical Center and the Cleveland Clinic Foundation in conducting a workshop exploring flow-induced blood trauma in medical devices in September 2001. The presentation topics included testing for red blood cell mechanical fragility on the bench, identifying factors which affect hemolysis testing (e.g., animal-to-animal variability, hematocrit, temperature), and evaluating medical device testing from a regulatory perspective. Important areas of research identified by the workshop participants included the effects of medical devices on white blood cells and platelets, blood clot formation and release from devices (i.e., thrombosis and embolization), visualization of flow around devices, and the increasing role of computational fluid dynamics in complex medical device design.

Interlaboratory Comparison of Heart Valve Fluid Mechanics

Key words: prosthetic heart valves, left heart simulator, pulse duplicator, fluid dynamics

The evaluation of prosthetic heart valve hydrodynamic performance relies on the use of a left heart simulator also known as a pulse duplicator. Manufacturers and test centers have developed various pulse duplicators and associated instrumentation. Recently, the concurrent need to update both the FDA premarket review guidance and the existing ISO international standard for prosthetic heart valves have prompted a study of the current test technology. The goal of this study is to understand the interlaboratory consistency of current test technology associated with the two primary hydrodynamic measures of heart valves -- pulsatile flow pressure drop and regurgitation. These measures are necessary in order to compare the performance of different valves or valve designs.

The collaboration, coordinated by OST labs, includes the pulse duplicators used by several manufacturers and test centers in addition to two left heart simulators maintained by OST. OST has developed and finalized protocols. These call for a round-robin evaluation of test valves. The test valves used to evaluate the measurement systems were obtained from the participating manufacturers and then first evaluated by OST. They will be circulated to all participating laboratories for testing and then tested again by OST. OST will perform the analyses and report the results.

Design and Optimization of a Flexible System for Digital Particle Image Velocimetry Fluid Flow Analysis

Key words: flow visualization, Digital particle image velocimetry (DPIV), standard test method, validation

Digital particle image velocimetry (DPIV) is a flow visualization tool that provides for a quantitative 2-D velocity vector mapping of flow patterns. The technique uses clear plastic models to examine the effect of specific medical devices upon blood flow in the body. This measurement technique can identify zones of flow stagnation or high shear stress, either of which can lead to adverse effects. Flow stagnation can cause thrombosis, embolism, and stroke. Excessive shear causes hemolysis, that is, ruptured red blood cells.

DPIV requires two high-intensity light pulses to illuminate fluorescent beads flowing through the region of interest. These pulses are separated in time by a fraction of a second. The changes in bead positions observed in the two images provide the information needed

to compute fluid velocity. Short intense pulses are needed to freeze the motion of the particles. Laser pulses coupled to the model by fiber optics provide the most practical method of illuminating the model system. However, the intense pulses approach the damage thresholds of the fiber optics.

Three commercially available solid silica core fiber optic links were evaluated for providing a flexible laser illumination sheet for DPIV applications. In addition, the peak power density damage threshold was determined. The damage threshold varied from 2.1 GW/cm² for the smallest 100 μm fiber to >3.3 GW/cm² for the largest 365 μm high power delivery fiber. These three fibers are marginally useful for DPIV applications. To improve power delivery, OST began testing a new fiber link with potentially better laser power delivery capability. Scientists used a hollow glass taper coupled to a specially coated hollow fiber waveguide with a hollow air core diameter of 300 μm and coated for transmission @ 532 nm. This new fiber technology can handle peak power density levels in excess of 10 GW/cm².

Safety of Electrical Stimulation to Neural Tissue

Key words: nerve, brain, computer model, high frequency, neurology, electrical stimulation

Many organ-assist devices employ electrical stimulation to alter physiology and treat pathologies. Recently, a number of developing electrical stimulation devices initiated paradigms for rapid-rate neural stimulation. The safety of such stimulation, which is beyond the physiological range of neuronal activation, has not been studied. In FY 2001, OST scientists examined the effects of rapid-rate stimulation in computer-modeled and real nerve cells. Stimulation at these rates will induce nerve depolarization and the irregular firing of nerve impulses. This was shown by the model and by actual experiments. The work positioned the Center to anticipate safety issues early, and it was applied to a broad number of regulatory reviews, several international standards, and several FDA guidance documents.

HOST RESPONSE

Biomaterials in contact with human tissues may have direct or indirect adverse (toxic) effects. The various types of toxicity may be time-limited and result in minimal and reversible effects, or may be longer-lasting resulting in serious tissue damage. The OST program in Host Response to Medical Devices consists of focused laboratory studies and risk assessment approaches to identifying causal agents, understanding the means and mechanisms underlying adverse biological effects, and developing approaches to minimizing their consequences. These studies make use of cutting edge technology and deal with serious emerging health issues. They encompass methods development, biomaterials safety evaluation, and forensic studies, as well as longer-term hypothesis testing to investigate unanticipated adverse effects of new materials and devices. The aim is to provide the Center with independent, timely and authoritative scientific support at various points in the Total Product Life Cycle.

I. Biomaterial Effects on Immune System

Development of a Standard Methodology for Testing for Classical Pathway Complement Activation in Serum by Solid Materials

Key words: complement activation, classical complement pathway, medical materials, immunotoxicology, standard

OST scientists conducted experiments to acquire data and develop procedures for a standard methodology capable of screening medical device materials for classical pathway complement activation in human serum. Complement activation is a potential hazard when a patient's blood contacts medical device materials. Although the expected pathway for activation, should that occur, is via the alternative pathway (not requiring antibodies), some medical devices may directly or indirectly activate complement by the antibody-dependent classical pathway. OST scientists have previously developed two other related standard methodologies: 1) testing for complement activation by either pathway (ASTM F1984-99), and 2) testing for complement activation by only the alternative pathway (ASTM F2065). In the present methodology, C4-deficient guinea pig serum was used as an indicator to test for the presence of the classical-pathway specific component C4 following exposure of human serum to a device material. This standard methodology will be submitted to ASTM for acceptance as a voluntary standard useful to industry in testing materials for use in new blood-contacting medical devices. In addition, it will help CDRH

reviewers determine validity of data submitted by applicants claiming lack of immunotoxicity of device materials.

Development of Assays for Determining Complement-mediated Immunotoxicity of Cardiovascular Devices

Key words: complement, restenosis, balloon angioplasty, porcine, immunohistochemistry, immunotoxicology, serology

OST scientists initiated immunohistochemical and serological investigations to evaluate complement activation in serum or deposition of complement components in coronary arteries of pigs during experimental angioplasty. Complement activation is an immediate result of tissue injury and can be amplified by materials present on medical devices. *Neointimal hyperplasia* (overgrowth of the attaching artery) is a common outcome and failure mode of cardiovascular device interventions. Activation products of complement may play an important role in regulating neointimal hyperplasia. Serological assays include the development of a porcine-specific C3a ELISA, and an ELISA for C5b-9 is currently being developed. In parallel, an immunohistochemical assay was established to detect porcine C3 in formalin-fixed preparations in arteries. Preliminary data suggest that porcine coronary arteries treated by balloon angioplasty may be subject to complement deposition, while arteries not injured by balloon overstretch are not. These data will be extended by appropriate time course studies in several pigs. Determining the immunotoxicological basis for adverse outcomes in the porcine model may provide a predictive model for adverse events in humans undergoing similar cardiac interventions. These studies may also assist in designing improved cardiovascular devices.

Autoantibody Responses Induced by Silicone Gel and Oil

Key words: autoantibodies, silicone gel/oil.

The goal of this project is to develop animal models for evaluating potential adverse immunological effects of implanted biomaterials. The initial study investigated the production of autoantibodies in female Sprague-Dawley and Dark Agouti rats injected with silicone gel from a breast implant. This study demonstrated the presence of anti-collagen antibodies in the serum of rats injected with dimethylsiloxane oil alone or a gel/oil mixture. To repeat and confirm these results, rats were injected at 5-8 weeks of age with an emulsion of silicone gel isolated from a breast implant and medical-grade 20 cs

dimethylsiloxane oil, or 1000 cs dimethylsiloxane oil alone. Incomplete Freund's adjuvant plus collagen I was used as the positive control and saline alone as the negative control. These injections, following the original protocol, were placed in the right mammary area of each rat. Serum samples are being collected from the tail vein of each rat at intervals of 2 weeks, 4 weeks, 8 weeks, and then every 28 days for 18 months. The samples will be analyzed for autoantibodies to rat collagen and to nuclear antigens.

Cytotoxicity of *In Situ* Polymerization of Medical Devices

Key words: *in situ* polymerization, cytotoxicity, standards

The current biocompatibility standards, ASTM (F748) and ISO (TC194-10993-1), describe methods for testing cytotoxicity of medical devices that are in a final polymerized form and not suitable for devices that polymerize *in situ* and have tissue contact. A method to make contact between the polymerization device and the test cells was devised. Cytotoxicity tests on a series of *in situ* polymers were performed and the information published. Application of the *in vitro* tests will aid ASTM and ISO in adapting current standards to assess the safety of these *in situ* polymerization devices.

Endocrine Disruption by Medical Device Materials

Key words: endocrine disruption, women's health, bisphenol A, hazard analysis, mode of action, development of standards

CDRH is concerned with the potential for certain medical device materials (including tissue engineering medical products) that adversely affect women's health, by mimicking or interfering with endogenous hormone actions. OST scientists, in collaboration with researchers at George Washington University, are improving the current standard assay for estrogenic activity of materials (currently under revision by ICCVAM, to which OST contributes expert knowledge). OST scientists have amplified the current assay by including key biomarkers of exposure that make it more specific and sensitive, and they have applied this assay to evaluating bisphenol A, a controversial plasticizer. Results of these studies have been published in peer-reviewed journals. One paper was honored as the journal's "Highlight Paper of the Month."

II. Genetic Technologies

OST is developing expertise in genomic and genetic technologies in preparation for the submission of devices based on these technologies. OST collaborated with external biotechnology laboratories to aid keeping pace with technological development. Two projects, one in genetics and one in genomics, are also providing new approaches to understanding host responses to medical devices.

A p53 Mutation Assay for Evaluating the Cancer-Inducing Potential of Medical Device Materials

Key words: genetic testing, p53 gene, cancer risk, microarrays, gene chips

Sequence changes in the p53 gene are the single genetic change most commonly found in cancer. An assay to directly measure these interactions, as a preclinical test for cancer risk assessment, is being developed. Such an assessment is a requirement for all new device approvals. Major progress was made in methods development to make a yeast reporter gene assay practical for screening of device materials. In particular, recovery of p53 mutants was enhanced from 2.5 times background (published data on original assay) to 100 times background in an OST laboratory. Collaborators on this project will aid in the genetic analysis of mutants by traditional sequencing, hybridization on microarrays, or analysis by electronic DNA chips.

Development of a Diagnostic Gene Expression Microarray for Type I Allergy Using Transcriptome Profiling

Key words: genomics, differential gene expression, latex allergy, microarrays

Genomic or gene expression technologies represent a new way to characterize the physiology of a cell or a person, most often in comparison with another condition. OST has established a genomics laboratory capable of differential gene expression technologies using several instruments. Funding was obtained from the Office of Women's Health for a genomics project in which gene expression comparisons are made in men and women who are either allergic or not allergic to latex. The patterns may yield differences that could be used as a basis for a diagnostic test for latex allergy and provide information related to the cause of this adverse response. The laboratory has been set up to provide the capability for

validating microarray technologies using more traditional differential display and real-time PCR measurements.

III. Tissue / Material Interactions

Development of an *In vitro* Test Method for Studying Human Endothelial Cell Monolayers Undergoing Immunotoxic Reactions Associated with the Use of Cardiovascular Devices

Key words: HUVEC, endothelial cells, immunotoxicity, cardiovascular devices

OST scientists have developed a fluorescence-based *in vitro* methodology for determining cell function and intracellular calcium signaling in monolayers of human umbilical cord endothelial cells (HUVEC). Increase in intracellular calcium can change normal endothelial cell function, affect communication with smooth muscle cells, and be indicative of lytic cell death (necrosis) or programmed cell death (apoptosis). HUVEC monolayers are used as a model of the endothelial cells lining the inside of coronary arteries. During cardiovascular procedures such as balloon angioplasty, endothelial cells may be damaged or have their functions perturbed. These effects may subsequently contribute to overgrowth of smooth muscle cells (restenosis), with re-blockage of the coronary artery within weeks or months. Conditions of the HUVEC monolayer assay were optimized, including culture conditions, labeling with the calcium-sensitive dye Fluo-4, best procedure for determining Fluo-4 fluorescence using a fluorescence 24-well plate reader, and the use of different culture media necessary to test immunotoxic components such as complement and cytokines. This assay may be used to determine the role of specific blood-borne factors in risks associated with the use of cardiovascular devices. The procedure should be readily adaptable for studying endothelial cells from human cardiac arteries plus associated smooth muscle cells central to the critical problem of restenosis.

Tissue Engineering

Key words: tissue engineering, tissue engineered combination products, standards, research/technology assessment

An OST scientist served as Chair of the FDA Inter-Center Tissue Engineering Working Group, providing leadership in programs designed to develop guidance and planning options to the Center and Agency. These encompass 1) monitoring and assessing

technology, 2) evaluating applications in medical products, 3) developing standards for tissue-engineered medical products, and 4) education/training for Center/Agency review/research staff and the at-large scientific community. Several accomplishments have contributed to the knowledge base for the Center/Agency and have facilitated scientific and regulatory assessment of new biotechnology-derived and tissue-engineered combination medical products.

These projects have focused on addressing the scientific and regulatory considerations for new products, developing information for Center/Agency decision-making, and for developing policy regarding product safety and effectiveness issues. The focus has also been on analyzing products in review and under development; communicating information to the Center/Agency and scientific community through different mechanisms; educating Center/Agency staff and the research and development community through presentations, publications and short courses; and participating in the development of cooperative programs with other Federal agencies.

Standardization of Cell-Based Methods for Evaluating Natural Materials Used for Tissue Engineered Medical Products (TEMPs)

Key words: cell adhesion, histomorphometric

Cell adhesion assays are being developed which should assess the ability of cells to adhere to substrates (i.e., polymers and natural materials such as collagen), as well as to maintain the expected cell phenotype when cultured/grown on TEMPs substrates. Histomorphometric techniques, currently under development, will provide an additional quantitative assessment of cell characteristics on these substrates. Scientists will establish criteria to ensure the reproducibility of both the surface coating technique and the adhesion assay wash procedure, which use an in-house apparatus. To date, cell adhesion assay parameters have been established for cell concentration, dye concentration linearity range, and wash conditions. Preliminary data have shown a two-fold difference in cell adhesion to polymethylmethacrylate and ultra-high molecular weight polyethylene polymers.

This project has resulted in the formation of a Task Group within Division IV, Tissue Engineered Medical Products, to develop an ASTM standard for cell adhesion assays for tissue engineering.

Other work in the area of standards has resulted in a draft ASTM standard for characterizing Type I collagen, which is currently under ballot in the Division IV, and a publication in the New York Academy of Sciences summarizes two standards that have been previously approved by ASTM.

Medical Device Particles and Adverse Cellular Reactions

Key words: wear particles, implants, standard, titanium alloy

Wear particles may be released from failed devices or are formed at articulating surfaces of implanted devices. Particles may also be injected directly into the body for clinical purposes. A murine macrophage cell system has been used to study the inflammatory potential of particles. Data generated on the inflammatory potential of particles helped 1) serve as the basis of the voluntary consensus standard ASTM F1903-98 on evaluating the biological effects of particles, 2) provide good science for Health Hazard Evaluations, and 3) allow CDRH scientists to review Corrective Action Plan. Titanium alloy particles were examined in FY 2001, and the results were presented at two national meetings in 2001 (Society for Biomaterials; Gordon Research Conference on Biocompatibility) and at the FDA Science Forum.

Reducing Allergies associated with Latex-containing Products

Key words: latex, natural rubber latex, proteins, allergy, powder

Medical devices made of natural rubber latex (NRL) contain proteins that can potentially cause life threatening allergic reactions. The Division of Life Sciences in OST conducted research targeting reducing the sensitization-potential of these products. These efforts focused on 1) identifying proteins responsible for inducing sensitization, and 2) developing methods to measure proteins on finished NRL products. The new ASTM standard D6499 (ELISA Inhibition Test) was developed as a more sensitive assay for quantifying antigenic NRL proteins. In collaboration with other research laboratories, studies were conducted to correlate the ELISA Test with other known methods for NRL protein quantitation. OST continues to evaluate the role of glove powder and to quantitate the powder-bound protein. The OST research resulted in proposing a new regulation for maximum powder and protein level on medical gloves. Research in collaboration with the ASTM D11 working group is being conducted to develop an HPLC chromatography method for analyzing chemical accelerants used in the manufacturing of latex products.

Studies on Nanotechnology for Detecting Biofilms

Key words: biofilms, nanotechnology

The FDA Office of Science and Coordination funded an inter-Center project on the use of nanotechnology for assessment of biological hazards. The CDRH portion of this project was to assess the application of nanotechnology for the early events in biofilm formation on medical devices. This project included leveraging with Cornell University for the production of micro-cantilevers. While Cornell is fulfilling its obligations, cantilevers used in Atomic Force Microscopy (AFM) were used to obtain preliminary information. The results indicated that these probes detect the biofilm-related adhesion events occurring in the first 4 hours, whereas standard techniques cannot detect adherence until 8-12 hours.

COMPUTATIONAL MODELING

Continuing advances in computer technology now make computational modeling a powerful tool for evaluating a variety of problems for which the underlying mechanisms are understood yet analytic solutions are intractable. Product designers are making increasing use of such modeling for product development; OST is making increasing use of such modeling for product assessment. These techniques allow scientists to manipulate a wide range of variables without having to create a physical representation of each possibility.

A well-optimized complementation of clinical trials with computer modeling holds excellent promise for both reducing costs and increasing product quality. For example, computational techniques often provide the best available information about blood flow through cardiovascular devices such as blood pumps and heart valves. Small regions of stagnant flow become breeding grounds for thrombosis, a potentially fatal complication. The information derived from computational analyses can be used in design optimization to suppress these zones of stagnant flow beyond what can be detected via clinical trials.

The goal of OST's investigations is to develop techniques that will enable the analysis of products and provide basic insight into the roles played by individual variables on the final outcomes. There are two major areas of current investigation in OST's Division of Physical Sciences (DPS).

A Computer Model for Determining Velocities of Heart-Valve Leaflets

Key words: computer simulation, prosthetic heart-valve dynamics, heart-valve cavitation

The tip velocity of a closing heart valve leaflet is known to be a useful parameter for quantifying the cavitation potential of prosthetic valves. Unfortunately, measurements of the leaflet velocity are difficult to make, requiring sophisticated techniques and equipment. Full numerical simulations of the closing process are likewise very complicated. A simple procedure for determining leaflet velocity in terms of easily measured quantities is highly desirable.

In the case of rigid cavitation testers, approximations can be made which make a simple mathematical model feasible. In rigid cavitation testers and pulse duplicators, impulsive motion at the boundary (often an accelerating piston) produces large pressures and temporal gradients in fluid velocity near the valve, but relatively small velocities. Under these "impulsive motion" conditions, the pressure field satisfies Laplace's equation, i.e., determining the pressure field is essentially reduced to solving a low-frequency scattering problem. Leaflet motion is calculated by first solving Laplace's equation in the geometry of the test apparatus, using stationary leaflets at various angles. The resulting pressure "scattering coefficients" are then stored and used in a simple rigid-body analysis to determine the leaflet motion. Additional input to this rigid-body analysis is the ventricular pressure, which is easily measured, along with the leaflet properties.

The impulsive-motion model just described was used to analyze data from 12 tests of Edwards-Duromedics valves at the cavitation threshold. Experiments were conducted in the FDA cavitation tester, as part of a 1994 round-robin study. The average calculated closing time of 0.021 (+/- 0.003) seconds compared well with the mean time of 0.019 (+/- 0.005) seconds determined from videotapes. The mean computed tip speed was 2.6 (+/- 0.3) m/s, in agreement with published values. Application of the model to other valve types is under investigation.

Computational Studies of Vascular Grafts

Key words: vascular grafts, cardiovascular devices, artificial organs, computational studies

After nearly 40 years of development, devices to replace diseased arteries still do not perform perfectly, especially in small diameters. Failure of small-diameter vascular grafts usually occurs by a combination of thrombosis and intimal hyperplasia (overgrowth of the attaching artery) which occludes the vessel. Intimal hyperplasia has often been noted to occur preferentially at the downstream junction between the vascular graft and native artery. This suggests that a flow-related mechanism is at least partly responsible for the failure. Laboratory experiments in transparent models have shown that small differences in the stiffness or diameter between the vascular graft and native artery can cause the trapping of tiny particles used to simulate blood cells at the downstream junction. If this happens in patients, the trapping of blood cells can cause agglomeration of cells and release of biochemicals which might cause the observed thrombosis and intimal hyperplasia.

This complex situation is now being modeled in a computer simulation, where greater control over the experimental parameters and more detailed examination of the results are both possible. Preliminary results show that a diameter/stiffness mismatch at the downstream junction does indeed enhance the concentration of a dissolved constituent. If confirmed, this research will provide additional support to the hypothesis that minor geometrical abnormalities can affect the proper healing of a vascular graft through a flow-related mechanism. This project also demonstrates the usefulness of computer simulations in developing cardiovascular devices. Such simulations are expected to gain importance in the device applications that the Center receives in the future.

Predicting the Intraocular Pressure Following Pneumatic Retinopexy

Key words: detached retinal, perfluoropropane, sulfur hexaflouride

CDRH received a PMA for a new use of perfluoropropane gas retinal tamponade. In this technique a gas is injected to push the detached retina back into place. Once the retina is in position, cryotherapy is typically used to weld the retina in place for subsequent regeneration of the pigment epithelium. In the eye, blood gases diffuse into the bubble causing expansion, followed by desorption of the gases over a period of several weeks. During this period, elevations in intraocular pressure are possible, which could have long term adverse affects on the patients' vision. OST developed a mathematical model of the gas diffusion of the injected gas, blood gases, and pressure dynamics to predict conditions that could result in elevations of intraocular pressure. The model predicts the expansion and persistence of the gas, as well as injected gas compositions that minimize expansion

and pressure elevation effects. OST was also able to correlate molecular volume of different candidate materials with the diffusion rate in the eye.

The model has been submitted for peer-reviewed publication in *Current Eye Research* and a manufacturer has expressed interest in marketing the model to outside parties. This model will allow ODE to substantially reduce animal testing. The model can accurately track the non-expansive behavior of tamponade gas - air mixtures. Once the model is correlated in the rabbit, it can reduce the number of experiments needed to establish the persistence in the eye.

Predicting the Shelf Life of Dialyzers

Key words: polymer degradation, shelf life, dialyzers

OST developed a Monte Carlo model to predict the chemical degradation of dialysis membrane materials in storage. The model tracks changes in a population of molecules representative of the dialyzer membrane. The degradation process calculation is a two-step process: first the model uses a random number to select an individual polymer molecule out of the population; then a second random number is used to select the site on the molecule for the degradation reaction. After the reaction, the resulting fragment molecules are redistributed into the population, and population average properties are recalculated. The model has been applied to cellulose acetate and polyethersulfone materials. A shelf life of 2 years was identified for cellulose acetate dialyzers based on animal test results. Polyethersulfone work is still in the preliminary stages, since this polymer has a more complex degradation mechanism.

New methodology to predict polymer degradation will help CDRH and device manufacturers' predict chemical degradation effects based on chromatographic data acquired in short term experiments.

Performance Characterization of Accelerator Target Systems for Neutron Capture Therapy

Key words: radiation therapy, neutrons, cancer

Boron Neutron Capture Therapy (BNCT) is an investigational therapy for brain tumors that are refractory to current therapies. Boron Neutron Capture Synovectomy (BNCS) has

been proposed for treatment of rheumatoid arthritis. The continuing development of proton accelerator technology will result in greater clinical application of these therapies. Although BNCT is an active area of clinical investigation, dosimetric methods have not been standardized, making it very difficult to compare results of clinical trials to conventional treatments to assess efficacy. This project will help to standardize the methods used for BNCT dosimetry.

OST is studying neutron source design for clinical applications using computational modeling of neutron transport. During FY 2001, the models were extended to include the detailed physics of neutron sources available to OST. A model of a human phantom was used for analyzing radiation doses to several organs. OST developed detailed models of the neutron moderators used for its experiments. The researchers are developing *in vitro* models of BNCT using cultured brain tumor cells loaded with p-Boronophenylalanine (BPA). OST confirmed that the brain tumor cells concentrated the BPA to three times the external concentration and has signed an interagency agreement with DOD to use DOD facilities for experiments. During FY 2002, a significant computational effort will be devoted to the design of the shielding cave for the planned OST facility and scientists will continue dosimetric measurements and biological experiments on the DOD neutron source.

DEVICE PERFORMANCE ANALYSIS AND MODELING

Many device failures that occur are related to materials problems, both for implantable and non-implantable types of devices. The development of chemistry- and materials-oriented test methods and performance requirements for devices is important for studying and predicting device failure modes and establishing performance criteria that will help ensure device safety and effectiveness. Such test methods and performance requirements minimize the regulatory burden on the agency and industry through the development and use of consensus standards and/or Guidance Documents. The development of these types of documents, especially if minimum performance criteria can be developed, would greatly aid manufactures and reviewers alike and lead to improved products by preventing failures through known mechanisms. Alternatively, manufactures could certify conformance to these standards as part of FDAMA.

There are three major areas of focus for this program area. The first is assessing those devices that rely on chemical measurements or mass transfer for their

performance. The second is developing bench test methods and requirements related to mechanical performance, reliability, and materials changes, such as strength, elongation, gas mechanics parameters, durability, abrasion resistance, and corrosion resistance. The third is developing computer and animal models that simulate clinical conditions, which can be used to supplement bench data in predicting device clinical performance and failure modes. Included in this is the development of experimental pathology methods for evaluating device performance *in vivo*.

ODE is being provided with the extensive technical sections for a manufacturer's guidance for gaseous fluorocarbon retinal tamponades. As a result of this work, a computer-based biological model to better understand the mode of action, adverse effects, and the performance of the tamponade is being developed. With this model scientists are able to predict clinical adverse ocular pressures and the duration of the gas bubble in the eye from the molecular properties of the gas and conditions of use. Other biochemical and biological properties of the gases are being used in the construction of the guidance. Also, work is being done on *in vivo* polymerized medical devices in order to provide ODE with the technical and test sections for a manufacturer guidance document. Traditional testing according to ISO 10993 is of dubious applicability to these devices. The tests in the guidance need to relate the chemistry of the starting, intermediate and finished materials to the performance and biocompatibility of the device. Just completed is a three-center study of the performance of self-monitoring blood glucose meters. Four of the most prevalent meters along with three lots of test strips were evaluated against the hexokinase comparative method that was itself checked against a NIST standard reference serum. One hundred and fifty blood samples were used. Results were compared against the Clarke error grid and found to be clinically acceptable. This finding strongly supports CDRH's emphasis on user errors for these devices.

Work in the second major program area resulted in the development and validation of several standards for endovascular stents, which will be incorporated into guidance and help expedite product review in a very high workload area. Also, data were obtained on whether or not magnetic resonance (MR) imaging equipment adversely affects the performance of oxygen regulators. This work was undertaken in response to recent problems with projectile accidents and equipment malfunctions in the MR suite involving oxygen cylinders and other devices. It was determined that effects of MR on oxygen regulator performance are clinically insignificant and the results and methods will be published for the information of

the agency, health care workers and industry. Work in the third major area included development of an animal model for evaluating tissue engineered cardiovascular devices and explant pathology methods for evaluating tissue engineered vascular grafts. This work provided critical and timely information on methods for assessing the safety and effectiveness of these new and rapidly emerging types of technologies.

Endovascular Stents Standards Development

Key words: recoil; standards; stents; test method; vascular stents

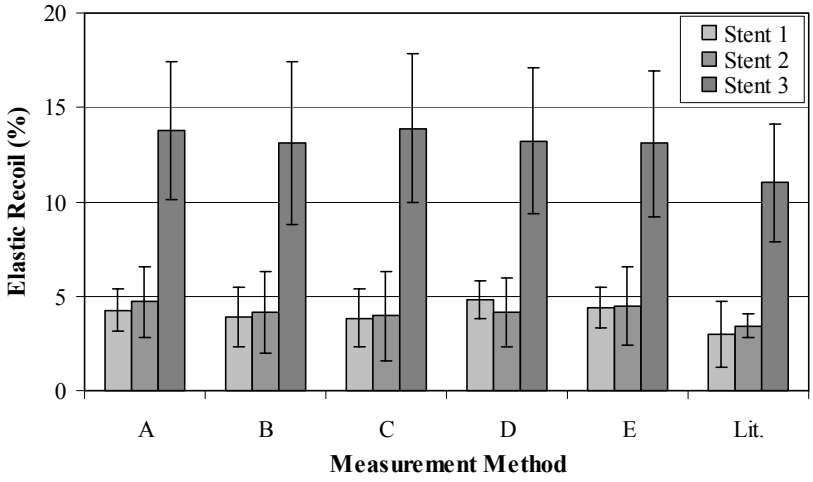

Fig. 1 The recoil of three stent designs was measured using five different test methods. Method A is the final, published ASTM method; Method B is a method described in an early ASTM draft. Literature values (from Barragan, et al., 2000) are shown for reference.

OST continues to lead the effort to develop consensus standards for endovascular stents. The goal is to develop a series of standardized bench tests that, together, may be predictive of clinical performance (see table) and facilitate premarket reviews for these devices. During 2001, the first two ASTM standards for stents, F2079 Test Method for Measuring Recoil of Balloon-Expandable Stents, and F2081 Guide for the Characterization and Presentation of the Dimensional Attributes of Vascular Stents, were published. OST engineers performed a critical laboratory evaluation of the published test method for recoil (**figure 1**) to determine if a) it could be implemented on most contemporary designs, b) the

results were repeatable, c) the results correlated with clinical experience, and d) the modifications to the method could improve the data (see bar chart). As a result of this effort, revisions to the published standard have been proposed and balloted.

The standards development activity continues at an aggressive pace, with six additional standards at various stages of development. These include test methods for fatigue testing, securement on the delivery system, radiopacity, longitudinal flex strength, and radial stiffness, and a guide for performing finite element stress analysis.

Bench Data vs. Clinical Outcome

Stent	Restenosis Rate	Recoil	Metal Area
GRII	43%	11%	16%
Wiktor	47%	8%	8%
Micro II	25%	7%	14%
Multilink	15%	5%	15%
Palmaz-Schatz	20%	5%	20%

Table 1

Promoted Ignition Testing of Medical Oxygen Regulators

Key words: oxygen regulator, fire, explosion, standard, ignition test

A promoted ignition test was developed with NASA to reduce the frequency and severity of fires that have been occurring in medical oxygen regulators. The test exposes regulators to an ignition event simulating worst-case conditions that occur clinically. Most recently, variations of one regulator model were tested to evaluate test method reproducibility and utility in assessing the safety of regulator design changes (**figures 2 and 3**). Scientists are also conducting round robin testing to facilitate finalization of the standard. Many manufacturers have revised their regulator designs to comply with the standard, and since then there have been no fires reported with such regulators.

Fig. 2 Oxygen regulator exploding during test

Fig. 3 Remains of exploded regulator after test

Mechanical Stability Analysis of Robotic Surgical Arm

Key words: robotics, robotic assisted surgery

In response to an ODE request, OST conducted a stability analysis of a robotic arm used in minimally invasive surgical procedures. After examining technical information and experimental data provided by the arm's manufacturer, OST performed an analysis of the arm's mechanical stability. Of particular interest was the arm's susceptibility to vibration when it was attached to the operating bed rails. Measurements of vibrational magnitude and duration that resulted from an applied force were taken at the arm's maximum and minimum stable configurations. Scientists conducted tests with a simulated bed railing in the laboratory and at the Bethesda Naval Hospital using actual operating tables. Analyzed results were forwarded to ODE with recommendations concerning the device stability.

This is one of the newest types of devices reviewed in CDRH. Based on the media coverage and manufacturer interest in remote surgical devices, it is anticipated that the laboratory support for this product application is the first of many to come.

The Effect of a 2T Magnetic Field on Flow Delivered by Oxygen Regulators

Key words: MRI, oxygen regulator, flow rate, magnetic field

Not too long ago, a 6-year-old boy undergoing an MRI scan was killed by a portable oxygen cylinder that was pulled into the scanner's magnetic field. Investigation of the incident led to questions about the operation of oxygen regulators in large magnetic fields in and near MR imagers. OST scientists obtained 17 oxygen regulators from several

manufacturers, of types used with portable “E” gas cylinders. Flow rates were measured outside the 5-gauss line, and at two worst-case locations at the entrance to the bore of the FDA MOD-1 2T MRI scanner where the static magnetic field strength is 0.45 T and the spatial gradient field is 200 gauss/cm.

Flow rates for some regulators were changed by the magnetic field, with some increased and some decreased, though the magnitudes of the changes may not be clinically significant. In general, for the regulators tested, researchers observed greater differences between labeled and measured flow outside the magnetic field than differences between measured flow inside and outside the magnetic field. In some regulators, scientists observed a definite attractive force exerted on the regulator, though no force was great enough to pull the oxygen bottle from their hands. Interestingly, the flow rates of these regulators were not altered by the magnetic field more than the flow rates of the other tested regulators that did not exhibit an attractive force. The test results demonstrate that it is not possible to make general conclusions about the effects of large magnetic fields on oxygen regulators. This lack of a consistent effect is valuable information for the regulator users and manufacturers.

Comparative Ocular Analyses in an Animal Model of Diabetes Mellitus

Approximately 16 million Americans have diabetes mellitus, a complex group of syndromes that have in common a disturbance in the oxidation and utilization of glucose, which is secondary to a malfunction of the beta cells of the pancreas. There are at least two types and several subtypes. Type I (juvenile) or insulin-dependent diabetes mellitus (IDDM) is more likely to develop early in life, requires insulin injections to control the hyperglycemia, and accounts for 5-10% of all cases. Type II (adult) or non-insulin-dependent diabetes mellitus (NIDDM) is related to some "inappropriate" insulin secretion, occurs in 90-95% of the diabetic population, and is often well controlled by diet. Approximately 60% of the new cases are diagnosed in women. The prevalence of diabetes is higher in Native American, African-American (reportedly 50-60% higher), and Hispanic women than in white women. Thus, these women are at greater risk of developing long term complications. The complications of diabetes include heart disease, stroke, high blood pressure, kidney disease, nervous system disease, amputations, dental disease, and complications during pregnancy.

One of the most threatening aspects of diabetes mellitus is the development of visual impairment or blindness consequent to cataract formation, retinopathy or glaucoma.

Diabetes affects the (outer) lens, middle (vitreous), and inner (retina) areas of the eye. The incidence of cataracts is greatly increased over the age of 50 years, slightly more so in women, compared with non-diabetics. Rates of cataract formation are often 50% higher in NIDDM than in non-diabetic persons. The elevated glucose concentrations, seen in diabetes, equilibrates between the lens and the aqueous surrounding it, leads to shifts in water that alters the shape and the opacity of the lens. In retinopathy, problems develop as a result of fluid leaking from blood vessels into the eye or abnormal blood vessels forming in the eye. In either case, vision can be affected. If retinopathy is not found early or is not treated, it can lead to blindness. There are often no symptoms of retinopathy until the damage has occurred. Animal models are needed to study the progression and end organ effects of diabetes.

Psammomys obesus or the fat sand rat (sub-family- Gerbillinae; Family- Muridae) is a common rodent in the Middle East, inhabiting the semi-arid regions with salty soils from Algeria to Saudi Arabia **(figures 4a, 4b, 4c)**. It has been introduced into the laboratory for special studies on diabetes and renal function. This animal is unique in that it develops mild to moderate obesity, hyperglycemia, and the complications of diabetes such as cataracts, pancreatic atrophy, impaired renal function and ketoacidosis by dietary induction. The rodent also naturally develops otic cholesteatoma, spondylosis and intervertebral disc degeneration. OST has successfully completed pilot studies that demonstrate the anatomical and physiological similarities between P. obesus and the human diabetic.

The studies proposed will employ noninvasive spectroscopic techniques to record biochemical changes associated with the progression of a subject from normal to diabetic. Experiments will be based on a near-infrared diode laser, a unique animal model, ophthalmic instrumentation, and use of multi-variate statistical methods to delineate correlations between optical spectra and traditional indicators of diabetes progression (progression of cataract, glucose intolerance, and pancreatic function). Blood glucose and insulin levels of the animals will be closely monitored, and relevant ocular structures will be analyzed with light and electron microscopy. OST scientists propose that measuring the molecular changes in an animal model during the development of diabetes mellitus using this combination of blood measurements, *in vivo* optical spectroscopy, and tissue microscopy using the rodent, Psammomys obesus, will enable unprecedented documentation and correlation of the progression of the diabetic ocular pathologies.

Fig. 4a. Adult female sand rat (6 months old) and pup (3 weeks old)

Fig. 4b. Sand rats (8 months old) with (right side) and without (left side) cataracts

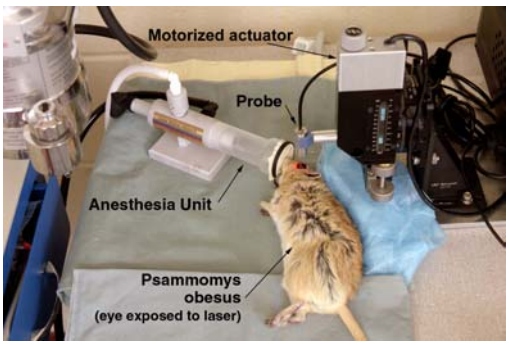

Fig. 4c. Close-up view of experimental set-up for prototype dynamic light scattering ocular probe, sand rat and anesthesia unit.

Large Animal Models of Vascular Disease and Therapeutic Device Interventions

Key words: minimally invasive techniques, vascular disease, angioplasty, radiofrequency ablation, preclinical animal models

CDRH has established a Laboratory of Large Animal Research to develop and study models of cardiovascular disease and therapeutic device interventions. OST scientists are using the lab to study the response of the coronary and carotid arteries to initial balloon angioplasty injury and then to subsequent re-intervention with angioplasty or stents for the treatment of restenosis. Results to date indicate that both animal gender and hormone state have a strong influence on the proliferative response to injury. The proliferative response is much greater in males than in females. Removing the ovaries, as a model of female menopause, results in a response similar to that seen in the males.

OST scientists are also examining the biophysics of radio-frequency ablation for the treatment of hepatic and renal tumors. The relationship of ablation volume to blood flow is being investigated along with the electrical properties of tissue. The research goals include improved understanding of both the mechanisms of action and the failure modes for these interventions. Results to date indicate that decreasing renal blood flow significantly increases the size of the ablation lesions attained in the kidney.

Physiologically Based Pharmacokinetic Modeling for Device Applications

Key words: bisphenol A, octamethycyclotetrasiloxane, pharmacokinetics

OST has developed several pharmacokinetic models to predict the bioavailability of chemicals exposed during medical device applications. In the past, these models have included degradation products from implanted materials, exposure to dialysis reuse degradation products, and ultrasound contrast agents. In the past year OST scientists developed models for exposure due to inhalation or implantation of octamethycyclotetrasiloxane (D_4) and inhalation, oral, or implantation bisphenol A. The bisphenol A model currently under development will also include a pharmacodynamic model to predict disruption of estrogen binding to plasma proteins albumin and sex hormone binding globulin.

The expertise of OST scientists in predicting the bioavailability of degradation products is useful in assessing the risk of new device applications.

MATERIALS STABILITY AND DEGRADATION MECHANISMS

The ability of a medical device to perform 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 the medical devices are safe and effective. In order to achieve this goal, this program area focuses on the development of 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.

The tasks undertaken within this program area vary depending on Center needs. The following narratives describe several program elements that have recently been completed and the effects of the laboratory undertakings on the regulatory decisions made by the Center.

As the final step towards the prevention of adverse effects brought on by excessive aging of dialysis cartridges used in hemodialyzers, an experimental and a Monte Carlo computer modeling study of aged dialyzers was completed and published. The results, based on dialyzers as old as 13 years, supported an acceptable shelf life of more than three years. This confirms ODE acceptance of the 2-year manufacturer's expiration date. Also, working with ASTM D11.40 and the Akron Rubber Development Laboratory, an approach and, ultimately a standard for accelerated aging of gloves, to determine shelf life has been devised. This will help make the determination of shelf life less burdensome in that short-term data will be used to predict long-term behavior. A study of the effect of nonoxynol-9 (N-9) on polyurethanes used to make condoms in response to concerns from ODE and Compliance about the effect of N-9 on the shelf life of such products has been completed. Effects on mechanical properties were found to be short-term and compensation by adjustment of initial properties can be done. Biological modeling and animal experiments in cooperation with CFSAN are underway to assess the

effect of ingesting bisphenol A. Bisphenol A is a component of food can coatings and dental sealants and leaches from these materials in very small amounts. This work is intended to help resolve arguments about the level of no effect. If this level were to be changed the public health impact could be very great. OST used its expertise in analyzing device performance to develop, in conjunction with NASA laboratories, test methods that helped evaluate the potential for certain oxygen regulators, used in home health care and emergency medical situations, to catch fire. The resultant fires could cause serious injury to the patients and health care providers. As a result of this work, manufactures are changing their designs to be more robust and less likely to ignite. The work on the reuse of single use medical devices described below lead the effort in reclassifying these types of devices, as well as drafting new regulations. Further materials research related to Materials Stability and Degradation is discussed in the section on reuse.

Shelf Life of Medical Gloves

Key words: shelf life, gloves, covalently cross-linked, accelerated aging, creep, modulus

OST has been working with the expiration dating working group of ASTM (D11.40) to develop an accelerated testing method to allow manufacturers to provide a tentative but accurate shelf-life level on glove packages. Since the thermal and/or oxidative degradation properties of covalently cross-linked materials (e.g., latex) often disobey simple Arrhenius or Q_{10} rule, studies of temperature aging on latex glove fingers are underway to determine the acceptability of various accelerated tests. Creep and modulus are being measured under forces comparable to those developed during actual use. The methodology developed in this project can serve as a platform to evaluate the completeness of the data, and thus, the appropriateness of a manufacturer's claim to predict a safe shelf life for devices (not just those made of latex) that challenge Arrhenius.

Determining the shelf life of materials is essential to the safe use of medical devices. This gives manufacturers a means for determining a shelf life in a short period of time.

Explant Pathology of Cardiovascular Devices

Key words: decellularized carotid artery, extracellular,

The purpose of this study was to evaluate the morphologic findings in small-diameter freeze-dried, decellularized carotid artery grafts implanted in goats as carotid artery interposition grafts for 6 to 7 months. Unimplanted decellularized carotid artery grafts did not contain intact cells; however, remnants of smooth muscle cells were present in the media. The extracellular matrix was well preserved. All decellularized grafts were patent at explant, without significant dimensional changes or aneurysm formation. Their luminal surfaces were lined by a thin *neointima*, consisting of myofibroblasts, collagen, and a discontinuous layer of endothelial cells. Histologic evidence of calcification was not observed; however, electron microscopy showed calcification of minute remnants of cell membranes. Inflammatory cells were not present in the graft wall. Host cell migration was greatest in the *adventitia* along the length of the graft. The migration of host cells into the media was more apparent close to the anastomoses, forming cellular nests rich in extracellular proteoglycans, while cell migration into areas subjacent to the lumen was minimal. Ingrowth of host blood vessels was not observed. These results demonstrate satisfactory structural and morphologic features of a decellularized carotid artery small diameter graft implanted for up to 7 months.

Assessing the Threat of Damage to Medical Devices and Packaging from Irradiation by the US Postal Service

Key words: Gamma sterilization, e-beam irradiation, polymer degradation, device packaging, radiation effect, free-radical generation

The Office of Compliance has been tasked by ORA/ORO to examine the impact of radiation sterilization of medical devices shipped via the mail. OST has accepted the responsibility to find and assemble published data regarding the radiation damage thresholds – for both the electron beam and gamma sources – for the various polymers used in either the packaging or the devices themselves. The collection of available literature, lab reports, or contractor lab reports will become the starting point for deciding what studies will be initiated to fill in the gaps in the matrix of material vs. the radiation source. These complications will be shared with AAMI's Committee on Radiation Sterilization as well as other affected trade associations.

These changes in mail security have become a new issue with the assurance of medical device safety and effectiveness under the responsibility of CDRH.

Mechanical Properties of Polyurethane Film Exposed to Solutions of NONOXYNOL-9 Surfactant and Polyethylene Glycol

Key words: polyurethane, nonoxynol 9 (N9)

Polyetherurethane condom properties (swelling, annealing shrinkage, tensile strength, strain to failure, modulus, creep, Tg, diffusion kinetics and absorption) were studied after exposure to solutions of N9 spermicide in PEG-400 for various times. As the N9 concentration increased, large amounts of N9 were absorbed and the mechanical properties decreased due to plasticization rather than hard segment domain disruption. Shelf life is not an issue since most of the absorption and decrease in mechanical properties occurred within the first 20 hours after soaking. Anisotropy in properties suggests that the condom should be cut to optimize these property-orientation relationships.

The methods and results, unavailable in either the literature or in document submissions, have been used by ODE in requests for additional information in reviews and will be used in evaluating new condom materials and lubricants.

MEDICAL IMAGING EVALUATION

A wide variety of new digital imaging and display devices is under development by academia and industry, with a broad range of performance characteristics. The Center thus requires new/improved guidance for the evaluation of such devices. To this end, OST 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.

OST scientists are engaged in the development of appropriate methods for the evaluation of 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. OST scientists provide

reliable, quantitative laboratory measurements of imaging system characteristics to the imaging research community. OST scientists are also elucidating the fundamental mechanisms underlying the interaction between the image-forming radiation and the anatomy being imaged.

These investigations inform the Center's regulatory decision-making on new digital image devices. The expertise developed through this program is being applied to the review of PMAs for ultrasound bone sonometers and new digital radiographic imaging systems. This program contributes to the development of premarket guidance documents including "Information for Manufacturers Seeking Marketing Clearance of Digital Mammography System" and a guidance document on preclinical requirements for bone densitometers. OST scientists are applying their expertise to the development of a CDRH web site on CT, 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. Improved knowledge of the fundamental imaging mechanisms will lead to an understanding of the sources of variability in imaging data. Having that, inter-machine and inter-institute measurements can be corrected, leading to absolute, quantitative measures which can then be codified through a measurement standardization process. The x-ray spectral measurements program provides a source of otherwise unavailable data to the entire mammography research community for use in developing new equipment performance standards as digital mammography develops, special procedures and test equipment for MQSA, and will be used to inform decisions on marketing clearance for new products and in compliance actions."

OST scientists develop consensus evaluation methodology for diagnostic medical imaging systems such as mammography and other film-screen x-ray systems, computed tomography, nuclear medicine, diagnostic ultrasound, magnetic resonance imaging, and digital imaging including fluoroscopy and digital mammography. The goal of the program is to characterize and optimize medical imaging systems and components through application of quantitative measures of imaging performance and dose. This program also supports development of mammography equipment standards and special procedures and test equipment for MQSA.

Digital Image Display System Evaluation

Key words: digital radiography, soft-copy display, cathode-ray tube (CRT), flat panel, active-matrix liquid-crystal display (AMLCD)

The purpose of this project is to develop measurement and analysis procedures to evaluate the performance of image display devices for digital diagnostic imaging systems. While CRT-based monitors are currently the most commonly used devices for soft-copy display, flat panel monitors using AMLCD technology are entering the marketplace for medical image display applications. These devices exhibit a strong orientation dependence of brightness and contrast as well as significant sub-pixel structure. Both of these effects require developing new measurement and analysis methods for evaluating flat panel displays. These new methods and the data they produce are essential to the science base on which regulatory decisions are made.

During FY 2001 efforts were directed toward comparing a variety of methods for evaluating the sensitometric, sharpness and noise properties of both CRT-based displays and a new AMLCD flat panel display. Normal and off-axis luminance for the flat panel were measured with a specially designed photometric probe with a very small acceptance angle. The results were evaluated by studying the display compliance to the DICOM grayscale function at off-normal viewing angles. Resolution and noise properties of both CRT and flat panel systems were measured using a CCD camera. Resolution was evaluated using line patterns as well as with the broadband transfer method. Noise was analyzed in terms of two-dimensional noise power and signal-to-noise ratios.

Imaging System Performance Evaluation

Key words: digital imaging, detective quantum efficiency, resolution, machine observer

OST scientists continued to extend the quantitative assessment of the dose and imaging performance of imaging systems from the analog to digital imaging domain. Specifically, the research included the following topics: evaluating inefficiencies in imaging performance using laboratory implementations, when possible, of the inefficient imaging system; investigating the validity of the underlying assumptions for imaging performance measures based on analog imaging systems; and bridging the gap between subjective evaluations using imaging phantoms and objective measures of imaging performance.

With respect to inefficiency in the image formation process, imaging systems comprised of a small detector which "looks" at a large area of a light-emitting phosphor with a lens coupling system are commercially available and have been the subject of premarket submittals. These imaging systems can be quite inefficient depending on the characteristics of the optical coupling. OST scientists set up a lens-coupled imaging system in the laboratory to use as a test bed to investigate the efficiency question. The laboratory system provided the ability to investigate when a system of this configuration starts to develop a "secondary quantum sink" as a result of poor optical coupling. Experimental measurements have been made of the large area gray-scale transfer, resolution, and noise properties of the imaging system at two different values of optical demagnification factor and three levels of x-ray exposure. The values of a fundamental measure of imaging performance, the detective quantum efficiency (DQE), calculated from these measurements demonstrate the significant increase in imaging performance when the demagnification decreases by a factor of approximately two. These data reinforce the need for a lens-coupled digital imaging system to be carefully designed to avoid low coupling efficiencies and the attendant decrease in imaging performance. These data have been and will be useful in premarket approval reviews for digital imaging systems using lens coupling as a component of system design.

The consensus measures of imaging performance such as the DQE, which are part and parcel of premarket submittals, are based on assumptions germane to analog imaging systems, i.e., noise stationarity or imaging system shift-invariance. Yet, researchers know that these assumptions are violated when considering digital imaging systems. OST began investigating the impact of these assumptions on imaging task performance through a series of computer simulations. Scientists used a 2-D Monte Carlo simulation of a digital x-ray imaging system including adjustable parameters for the lesion to be detected, the characteristics of the background noise, the size of the image pixel, and electronic noise. The steps in the simulation closely follow the physical image-formation process commonly encountered in a digital radiography system. The OST approach has no requirement for making assumptions about noise stationarity or imaging system shift-invariance. It is based on the spatial-domain evaluation of task performance for model observers previously shown to bracket human performance. Using simple signals with known characteristics, scientists compared observer figures of merit derived from the OST simulation with theoretical predictions and obtained excellent agreement. In addition to computer simulation, OST also purchased a representative digital detector for experimental verification of simulation results in the laboratories using an actual digital imaging system. Fundamental measures such as resolution, gray-scale transfer, noise, and DQE have already been made on this system. Beside the close association with the computer

simulations, these data have been and will be used to gain knowledge and to provide constructive input to the standards-setting organizations dealing with these physical parameters.

In the future, research will also include investigations on replacing the coarse human readings of imaging phantoms or the more sophisticated and expensive laboratory measurements on imaging systems with machine observers reading an appropriate set of test images at the clinical facility. As a start, OST scientists used a lens-coupled digital radiography system (described above) for machine-observer scoring as a task-based measure of performance. Estimates of observer performance in terms of signal-to-noise-ratio were obtained from one algorithmic observer (DC-suppressed matched filter) and from one analytic observer (pre-whitening matched filter) for the task of detecting a known object (CDMAM phantom) on a flat background. For the special case of a large object at the center of the field-of-view, estimates of observer performance were essentially the same whether based on analytic or algorithmic observer performance. OST intends to continue this research track using more realistic test objects and imaging phantoms.

As stated in previous annual reports, this work will open up new approaches to imaging system performance evaluation. For example, a good understanding of the impact of the digital image formation process should have some impact on the imaging communities' selection of consensus measures. The use of these new consensus measures will then provide descriptive information on imaging system performance in premarket submittals. Additionally, quantitative and precise measures at the clinical facility can replace the subjective evaluation of imaging phantoms such as the scoring of the imaging phantom currently used in enforcement of the MQSA program. (See the section on X-ray Physics Laboratory Studies, above.) Developing staff expertise in implementing these evaluation tools will provide for more informed product reviews of all types of imaging systems, not just digital imaging systems. In addition, a stable protocol for quantitative measures at the clinical facility can provide the Agency with the means of making quick, efficient, inspections to regulatory criteria at the facilities.

Some of the products of this research activity included a presentation and two posters at the SPIE 2001 Medical Imaging Symposium and a poster at the FDA Science Forum.

Ultrasound Bone Densitometry

Key words: ultrasound, bone density, osteoporosis

OST plays a significant role in the approval of PMAs for ultrasound bone densitometers. This is a new technology that is likely to undergo much technological evolution and regulatory activity in the near future. Currently there is a considerable lack of standardization among devices. Pre-clinical experiments, clinical trials, and theoretical analysis are important in understanding this technology and anticipating future trends. This project provides an independent source of data in OST in support of regulatory decision making. OST has explored fundamental mechanisms underlying the interaction between ultrasound and bone. These investigations increase understanding of how and why ultrasound bone densitometry is effective and therefore lead to better and more thorough reviews of these devices. This technology is currently entering an exciting new generation with the first device to perform ultrasonic *imaging* (rather than simply bulk measurements) of bone obtaining FDA approval in 2001.

In FY 2001, this work resulted in five refereed publications and six presentations at scientific conferences. The work included a clinical trial to investigate a new method (backscatter) for characterizing bone *in vivo*. In addition, theoretical modeling and experimental measurements (*in vitro*) regarding scattering, attenuation, and sound speed were reported. A poster describing a model for ultrasonic scattering from bone won the Cum Laude Award at the SPIE Medical Imaging conference in San Diego in February 2001.

X-ray Physics Laboratory Studies

Key words: x-ray spectroscopy, phantom,

The purpose of this project is to evaluate equipment and materials used in medical radiography and in quality assurance of medical radiography systems, to support OST research efforts, other Center programs, and the general radiology community, when appropriate. The conduct of this project requires establishing and maintaining the capability to generate x-ray beams typical of those used both for mammography and for general diagnostic radiography, as well as state-of-the-art capability for x-ray measurements, including high-resolution x-ray spectroscopy.

OST responded to increasing interest in the medical imaging community in the use of higher-voltage x-ray spectra for digital mammography and iodine-contrast-enhanced mammography, and the absence in the literature of measurements of such spectra for the common mammography x-ray tube anode materials. In FY 2000, OST initiated a program to measure spectra from all three anode materials used in mammography at tube voltages ranging from 20 to 50 kVp. That program was continued in FY 2001, and initial results were reported at the annual meeting of the American Association of Physicists in Medicine in Salt Lake City in July. Representative spectra from a rhodium-anode tube are shown in figures 5a and 5b.

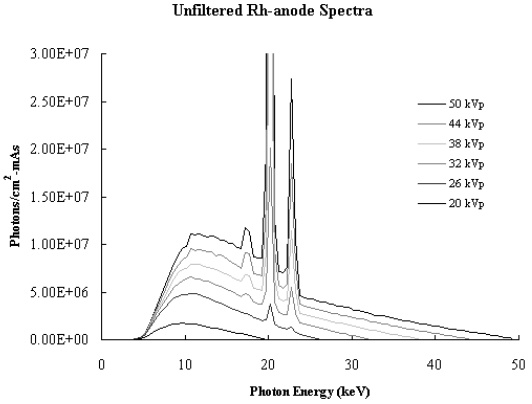

Fig. 5a. Measured x-ray spectra from a rhodium-anode mammography x-ray tube. Full-scale plot shows the relative intensities of characteristic lines and Bremsstrahlung continuum.

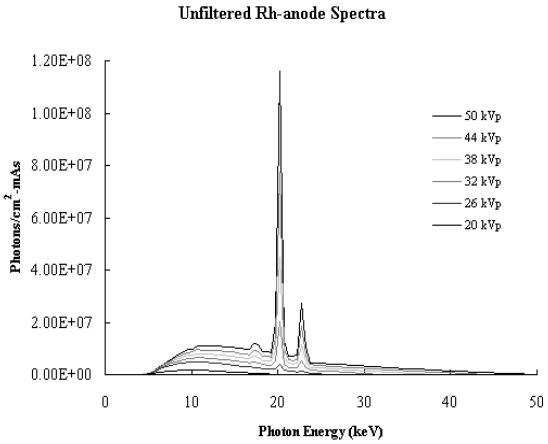

Fig. 5b. Measured x-ray spectra from a rhodium-anode mammography x-ray tube. Expanded scale shows the details of the Bremsstrahlung continuum.

The MQSA program requires that mammography facilities provide images of the phantom used in the American College of Radiology (ACR) Mammography Accreditation Program (MAP), and that the images allow the identification of a minimum number of test objects included in the phantom. Over the years, there has been a continuing criticism of the phantom on the basis that some of the test objects, particularly the small grains of crystalline matter that simulate microcalcifications, vary significantly from one phantom to the next. As part of an informal collaboration with the Pan-American Health Organization (PAHO), which is starting a pilot program to evaluate image quality and patient dose in mammography in Latin America, OST agreed to evaluate a group of 30 ACR MAP phantoms that were produced and purchased at the same time and that are representative of current production methods.

The approach is to produce multiple, extremely high quality images of the test object insert of each phantom using non-screen film, to digitize the films at high resolution, and to analyze the images by computer, using techniques already implemented. The techniques--the computerized analysis of mammographic phantom images (CAMPI) method developed by Chakraborty at the University of Pennsylvania and the RIT 315 ACR scoring routine (part of a commercial software package--both return a quantitative, numerical score for the visibility of each test object, so that the range of scores within a phantom and between phantoms for grains of the same nominal size can be determined. The range of scores on different films of the same phantom will provide information on the variability of the scoring process. The filming of the phantoms was completed during FY 2001. The analysis will be completed in FY 2002. The results will provide valuable information on the reliability of the phantom imaging portion of the ACR MAP and the FDA MQSA facility inspection program.

MINIMALLY INVASIVE TECHNOLOGIES

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.

OST's Division of Physical Sciences (DPS) is investigating a number of high-priority, minimally invasive technologies in order to assist Center reviewers in the timely assessment of manufacturers' submissions. Included in these technologies are 1) diffuse reflectance spectroscopy for optical diagnosis; 2) optical fibers, waveguides, and lasers for treatment; 3) thermal ablation using radio-frequency energy; and 4) ultrasound for imaging-based diagnosis and transdermal treatment. OST's investigations center on clarifying the mechanisms of interaction of the technology with the body and on developing meaningful performance assessment procedures. Such efforts are designed to identify the critical scientific questions early in the Total Product Life Cycle for new technologies, and to provide reliable ways to answer those questions.

In the area of optical diagnosis, DPS is developing analytic techniques to correlate optical tissue properties with diffuse reflectance data, evaluating fiber optic probes used in optical diagnosis, and developing mathematical models to assist in quantifying the distribution of energy within tissues. DPS is also studying laser therapy devices in order to elucidate the mechanisms of interaction of laser energy with tissue. This program contributes to the development of guidance on minimally invasive optical diagnostic devices and contributes to reviews of device applications for fluorescence diagnostic devices. Substantial contributions have also been provided to the FDA website on LASIK.

With respect to catheter-based thermal ablation, DPS is analyzing the temperature distribution in tissue during radio-frequency ablation for the treatment of cancerous liver tumors. The goals of this research are to 1) develop quantitative methods for establishing the safety of new ablation devices; 2) generate the biophysical data needed to improve the accuracy of models used to predict the size and shape of ablated regions; and 3) determine the relationship between the results of computational models and actual ablation devices. Already, these studies have allowed DPS to identify and resolve some of the critical issues in pre-market applications for ablation devices used for the treatment of soft-tissue tumors as well as those used for endometrial ablation.

Finally, advances in ultrasound technology make it increasingly attractive for both diagnosis and treatment, either through image guidance or through direct delivery of ultrasound energy. Often these new uses require outputs different than previously employed. Virtually all ultrasound submissions are reviewed for dosimetric acceptability by DPS scientists.

Heat Transfer Issues in Catheter Ablation Devices

Key words: ablation, heat transfer, cardiac, endometrial, oncology, radio frequency

This project is devoted to study how heat is generated and dissipated in medical devices that use radio-frequency (RF) energy to heat and destroy (ablate) diseased tissues. OST examined the physics of ablation *in vitro* using experimental systems and with computer simulations. The project objectives are to develop new tools for evaluating ablation devices, to determine the biophysics of ablation, and to develop appropriate safety and efficacy guidelines for the treatment of cardiac arrhythmias, liver/kidney tumors, and excessive endometrial bleeding. During FY 2001, OST scientists developed new test systems that use solid and liquid materials with electrical properties that simulate the properties of real tissues. The systems use laser instrumentation to measure temperature distributions in the tissue-simulating materials during radio-frequency heating with blood flow. This system generated independent data that was critical in deciding key issues at the FDA Clinical Panel for OB/GYN devices.

Temperature Rise in the Eye Due to Diagnostic Ultrasound

Key words: diagnostic ultrasound, eye safety, temperature rise

Previous work at CDRH showed that diagnostic ultrasound examination of the eye might produce high and possibly harmful temperature rises. Furthermore, it was shown that the TIS, the on-display estimator of temperature used by the FDA Guidance for Diagnostic Ultrasound Systems, can significantly underestimate the actual temperature during ophthalmic examinations. Therefore, the FDA implemented an output intensity limit for all eye exposures (50 mW/cm^2), which is lower than that allowed for general soft tissue exposure (720 mW/cm^2). This ensures that the temperature rise in the eye will always be below 1^o C. This overall very conservative and limiting restriction, however, does not allow for specific cases of transducer size, frequency, and focal length. It also does not allow for cases where, although the actual rise is greater than 1^o C, the TIS is greater still and is hence a conservative estimator of eye temperature.

Therefore, a more detailed theoretical analysis of eye temperature rise was performed to determine if a less restrictive set of output limitations could be developed and still ensure safety. It was found that for all types of eye exams, transducer diameters and focal lengths

currently used an upper intensity limit of 131 mW/cm^2, 137 mW/cm^2, 118 mWcm^2 and 168 mW/cm^2 (for frequencies of 7 MHz, 10 MHz , 15 MHz and 20 MHz, respectively) which provide for safe use of the device. No change in the overall limit (720 mW/cm^2) is needed for frequencies of 40 MHz and above. If specific focal lengths are taken into account, intensities may rise to as much as 584 mW/cm^2, 634 mW/cm^2, 619 mW/cm^2, for 7 MHz, 10 MHz, and 15 MHz, respectively. No change would be allowed for the 20-MHz case.

Low-Frequency Calibration of Medical-Use Hydrophones

Key words: ultrasound, exposimetry, hydrophone

OST's ultrasound laboratory is continuing to help develop the test methods and evaluate commercial measurement devices that manufacturers use to assure the safety of their biomedical equipment. Previously, OST engineers have shown that the low-frequency response of medical-use hydrophones is important for accurate pulse measurements, particularly of the peak rarefactional pressure, an important quantity for assessing the likelihood of cavitation onset. The Mechanical Index, a related quantity displayed on diagnostic ultrasound equipment, gives an indication of the potential for mechanical damage to exposed tissues. However, frequency response data below 1-2 MHz typically are not provided for commercial hydrophones designed for measurements in medical ultrasound fields.

To address this problem, OST developed a calibration technique in which broadband pressure pulses are used to measure the low-frequency response (0.2-2 MHz) of miniature hydrophones used in biomedical ultrasonics. A chief advantage of the technique is its ability to obtain broadband calibration data in a single measurement, as opposed to more time consuming single-frequency methods. However, expensive commercially available electronics are required for generating the high-voltage pulses needed, a disadvantage that makes the technique unsuitable for adoption by voluntary standards organizations. Therefore, OST has developed a new and economical voltage pulser that meets or exceeds the performance of the commercial device in this application. An initial design analysis has been published, and the final design is being completed for distribution to relevant standards setting organizations.

Noninvasive Optical Diagnostic Techniques

Key words: spectroscopy, mathematical modeling

Accurate *in vivo* optical property data are essential for understanding light propagation in tissue and for developing optical diagnostic techniques such as fluorescence spectroscopy. However, such information is scarce for many internal organs. Several studies for determining tissue optical properties have demonstrated the efficacy of diffuse reflectance measurements with illumination-collection fiber separations of up to tens of millimeters. But, these large separation distances are difficult to achieve for illumination probes used with gastrointestinal endoscopes. In FY 2001, OST scientists performed a preliminary study analyzing an optical property measurement system for the 300-750 nm wavelength range that uses small fiber separation distances. The approach involved the use of a neural network trained on radial profiles of diffuse reflectance generated by Monte Carlo simulations (incorporating accurate fiber apertures) to determine absorption and reduced scattering coefficients from experimental reflectance data. Results from 45 Monte Carlo simulations covering absorption coefficients from 0.1 to 30 cm-1 and reduced scatting coefficients from 5 to 25 cm-1 were used to train the neural network. Measurements were performed at a wavelength of 633 nm using solutions of Intralipid and ink as well as human skin tissue in vivo. Initial results indicated moderate agreement with optical property data in the literature. Simulation results indicated that increases in scattering and absorption accentuate the decay of radial reflectance distributions. Thus, the optimal fiber separation distances for determination of optical properties in the 300-750 nm wavelength regions are likely smaller than those which are optimal for near-infrared measurements performed in many previous studies. Simulations also indicate that errors of 10% or more in predicted reflectance can occur by not accounting for fiber aperture. Systems may also benefit from measuring light returning through the illumination fiber, a technique that has not been previously tested.

Minimally Invasive Fiber-Optic Biosensors

Key words: optical fibers, laser delivery, biosensors

OST scientists are continuing to investigate techniques for the delivery of laser radiation to tissues for optical diagnostic procedures. Optical fibers are becoming more useful in modern biomedical systems such as minimally invasive techniques for laser diagnostics, therapy, and optical imaging. A fiber optic-based biosensor system includes two principal

optical components: an effective laser delivery system and a sensitive sensor probe. In FY 2001, OST scientists worked to improve fundamental features of both optical-fiber biosensor components.

One area of study focused on the evaluation of an optical waveguide concept for efficient delivery of laser and x-ray radiation. It is based on a simple lens-free method for coupling laser radiation to optical delivery fibers. OST scientists utilized an uncoated glass hollow taper as a laser-to-fiber coupler. It is funnel-shaped and, utilizing the grazing-incidence effect, provides an efficient way of direct launching of laser radiation into delivery fibers.

A second area of study involved evaluating a novel approach for switching laser radiation on and off while being delivered into a precise tissue area. The method uses tissue activated optical fiber probes with specially shaped angled tips. It provides a safe method for laser delivery that includes only two states of tissue illumination: (1) off-state (no tissue illumination), when the fiber tip is out of the tissue area – the laser emission is back reflected at the angled tip due to total-internal reflection; and (2) on-state (tissue illumination), when the fiber tip is contacting the absorbing tissue area, and the laser energy is coupled into the absorber.

Low-Level Laser Therapy

Key words: laser therapy, biostimulation

The use of lasers for the therapeutic treatment of disease is growing. One type of photochemical laser application is known as photodynamic therapy. In this application a drug is first administered, and a selected wavelength of laser light is used to trigger a reaction that kills cancerous cells or stops a normally progressive disease. More people are now utilizing another photochemical application known as laser therapy (biostimulation or low-level laser therapy). This therapy does not use drugs but relies only on application of laser light to tissue. There is little knowledge of how these devices work to diminish pain or to accelerate wound healing. In trying to determine the mechanism of interaction of low levels of laser energy with tissues, OST scientists initiated a collaboration with the Uniformed Services University for the Health Sciences to use minimally invasive fiber optic sensors in an attempt to identify changes induced in tissue by laser light. This work will continue in FY 2002.

Lasers for Tissue Ablation

Key words: laser, ablation, cardiology

Lasers are increasingly being used to treat diseases via tissue ablation. Except for the excimer laser used in ophthalmology for photorefractive surgery, there are no guidelines for measuring the ablative performance of a laser device. In FY 2001, OST scientists began experiments to study the ablative performance of the laser devices used in percutaneous myocardium revascularization (PMR) and transmyocardial revascularization (TMR). There is a need to understand the mechanism(s) of the procedure and the science of the ablation process, as well as to develop guidelines for future PMA submissions. The therapeutic mechanism is not known, although a number of potential effects have been postulated. Depending upon the chosen mechanism, the ablative performance may directly influence the laser-tissue interaction and ultimately the patient's outcome. It is also important not to perforate the myocardium during PMR procedures. It is therefore critically important that the ablation rate be accurately known, so that during a PMR procedure the amount of laser radiation used will not cause a perforation. There are a number of different laser devices being investigated for TMR and PMR, including Ho:YAG, CO2, and excimer lasers. Each has different laser-tissue interactions. Subsequent changes to these laser devices will require the presentation of additional laser ablation data, in order to substantiate their equivalence without additional clinical trials.

OST scientists are continuing to develop laboratory phantoms that will ablate in a manner similar to swine myocardium. These phantoms may be made from swine and bovine skin, or polyacrylamide, or swine myocardium. Literature studies have shown that the ablative performance of pulsed laser devices depends upon the mechanical properties of the target tissue. The use of liquid plastics whose hardness or strength can be easily changed and molded into different shapes is being studied in order to simulate various tissues. In FY 2002, the mechanical properties of the phantom materials will be established, and ablation performance studies will begin. From these results, ablative performance guidelines will be developed which specify the ablative phantom's strength. It is expected that this will greatly reduce the variability in ablation performance that is currently found using heterogeneous animal tissues.

Tracheal Tubes

Key words: lasers, tracheal tubes, medical devices, patient protective covers, standards

In FY 2001, an OST representative was appointed as U.S. Delegation Leader for ISO TC 172/SC 9. This subcommittee continues to work on modifying the standard for determining the laser resistance of the shafts of tracheal tubes. When the standard was published in 1999, it was decided that a New Work Item [NWI] would be initiated to address comments which had been received when the document was circulated as a Draft International Standard [DIS]. The revised document is now at the stage of a DIS and will be circulated as a Final Draft International Standard [FDIS] in FY 2002. Work is also progressing on a standard for the laser resistance of surgical drapes and patient protective covers. The project group prepared a NWI that was circulated and approved as a DIS in the first half of FY 2001. The document will be circulated as an FDIS in FY 2002.

RADIATION BIO-EFFECTS

This program encompasses a collection of biological research projects needed to ensure that the public enjoys the benefits of modern medical and consumer technology without undue harm due to associated radiation exposures. Another goal of the program is to prevent unnecessary exposure of the population to radiation emitted from electronic products and to establish the scientific basis for regulatory decisions involving electronic product radiation.

The projects described below are complimented by standards development activities, particularly in the areas of nonionizing radiation exposures. The OST scientists responsible for this research are active in the revision of international standards and guidelines for ultraviolet, radio frequency, and extremely low frequency radiation.

Boron Neutron Capture Therapy (BNCT) promises the potential of becoming a major new modality for the treatment of brain tumors, whose therapy is currently problematic. Its clinical investigation and commercialization will raise a number of new medical device and drug-device issues for CDRH and CDER. OST has worked toward developing computational capabilities to verify dosimetric data submitted in IDEs and PMAs. One of the current challenges to bringing BNCT to the clinic is

the design of epithermal neutron beams which will result in safer and more effective therapy by maximizing tumor dose while minimizing normal tissue dose. Since reactor neutron sources are unsuitable for siting in hospitals, there is a need for computational design of beam generators employing particle accelerators. This requires extensive modeling of combinations of charged particle neutron sources, moderators, and reflectors to optimize the dose delivered to a tumor mass. Variables to be considered include tumor dose for various tissue depths and dose to normal tissues from boron capture, as well as proton recoil and nitrogen capture reactions and capturing gamma rays from the target structure. These calculations will provide guidance on desirable properties of neutron beams proposed for IDE's and can serve as a basis for the design of a future experimental facility. Until recently, powerful neutron sources were limited to a very few locations at existing nuclear reactors and thus not generally available for patient treatment. The marketing of a new generation of powerful nuclear particle accelerators, comparable in price to the accelerators currently used for radiation therapy, will soon make clinically useful neutron sources available for therapeutic applications.

Currently over 100 million Americans use wireless phones. This exposure of large numbers of people to radio-frequency radiation (RFR) is unprecedented. Data relating to the safety of wireless phones is currently inadequate to determine whether adverse health effects are likely to result from these exposures. A small number of chronic rodent exposures have been conducted which show no evidence of cancer in exposed animals; but one of these studies did indicate an increased number of lymphomas in susceptible transgenic mice. In addition, *in vitro* studies have been reported to show changes in enzyme activities that are suggestive of cancer-promoting effects. Another *in vitro* study showed an increase in micronucleus formation, a possible marker for epigenetic effects on DNA synthesis, in human cells exposed to wireless phone emissions. Research into the bio-effects and effects on medical electronics of cell phone use continues. OST developed and established a cooperative research agreement allowing FDA to better assess the possible health risks associated with mobile phone technology. Once the mobile phone industry has initiated this research, FDA will provide ongoing scientific and technical oversight of the research programs. OST research investigated some of the reported *in vitro* effects using an exposure system calibrated in terms of specific absorption rate. This research, along with extensive involvement in research with other laboratories, aids assessing published data that suggest the biological effects of exposure to radio-frequency radiation at levels relevant to wireless phone use.

OST studies of the utility of novel noninvasive and biomarker methods to test and standardize skin responses to ultraviolet radiation (UV) can provide data needed for revising the national and international standards in the area. Such research supports CDRH policies for ultraviolet lamps used in medicine and cosmetology, CDER policies related to sunscreens and photosensitizing drugs, and CFSAN policies in the area of cosmetics. FDA's policies regarding sunlamps have been repeatedly questioned by the consumers, the industry, and the medical community. OST research will include the collection of data on human subjects representing skin types I-VI and racial ethnic groups of (1) American Indians or Alaska Natives, (2) Black or African Americans, (3) Asians, (4) Hispanic or Latinos, (5) Native Hawaiians or Other Pacific Islanders, and (6) Whites. These data include changes in the skin properties following UV exposure assessed using two mechanical methods, four optical methods, one ultrasound method, and several biomarkers measured in the biopsies. OST data provide a solid scientific basis for improving the classification and testing of human skin sensitivity to UV.

Some UV-exposed skin cells do not die. Rather they acquire genetic mutations that can lead to skin cancer. Inhibition or failure of cells to die when too many genetic mutations have been acquired has recently been implicated as a mechanism for initiation and promotion of skin cancer by UV. *In vitro* laboratory data from cell exposure to UVA and UVB wavelengths separately, which are both emitted to different degrees from tanning lamps and, together, can be used to establish adjustments that should be made to existing UV risk assessment equations. Until recently, no risk assessment of tanning lamps for skin cancer could be accurately performed because only the action spectrum, i.e., data for the individual UV wavelengths, was known. The combined output effect on skin cancer from tanning lamps, i.e., UVA and UVB wavelengths, could not be established because a definitive biological endpoint to monitor in human cells was not established. OST data can be used to see if an additive, synergistic, or antagonistic effect occurs when UVA and UVB are combined together, as they are in tanning device emission. With this data, scientists will be able to complete a risk assessment because they will know the appropriate approach and equations to use in this tanning lamp situation.

Radiation scientists are assessing the utility of several testing methods for characterizing the effects of UV radiation on skin for potential use in the regulation of products such as sunlamps, tanning booths, sunscreens, and photosensitizing

drugs. In addition, a cross-agency effort was started to estimate the effect of exposure to ultraviolet radiation and implement methods to reduce exposures. The studies, initially funded by grants from the FDA Office of Science have begun to yield results that are useful in developing standards for determining UV exposures and for validating predictive models of tissue behavior when exposed to UV.

Responses of Human Skin to Ultraviolet Radiation

Key words: UV, tanning, melanin

OST is investigating the effects of UV exposure on human skin to update standards for UV-emitting/transmitting products. These studies involve exposing small areas of the backs of volunteers to single or repeated exposures and a broad range of measurements. Typical dermatological and tanning sources are used. OST has collected data on 93 subjects to date. The results indicate that melanin content may not be a sole factor in determining the UV sensitivity of human skin. Also, OST scientists demonstrated that both DNA repair and melanin production are more efficient in UV-resistant subjects than in UV-sensitive subjects. This indicates that DNA damage may not be a sole melanogenesis-stimulating factor. Preliminary data from the repeated exposure study indicate that UV burden to tanners can be markedly reduced without compromising the desired effect. These and other results of biomarker and noninvasive measurements provide quantitative data that will replace outdated standard criteria and guidelines.

Sunlamps and Sunbeds: Scientific and Regulatory Issues

Key words: sunlamps, sunbeds, melanoma

A review of CDRH's work on sunlamps was published in the book Sun Protection in Man (2001). This article discussed safety and regulatory issues related to sunlamps and sunbeds. The focus is on the indoor tanning industry within the United States, current U.S. and international regulations, possible changes to U.S. regulations, an assessment of the science base for regulatory changes, and a description of some of the U.S. and international standards organizations that are heavily involved with UV research and regulations.

The U.S. Food and Drug Administration is considering changes to its regulations that involve the content and design of its warning labels, redefining who is a manufacturer,

updating the recommended exposure schedule, updating the value of minimal erythemal dose (MED), and possibly using the non-melanoma cancer action spectrum for calculating recommended annual dose limits.

Ultrasonic Characterization of Skin Following Ultraviolet Light Exposures

Key words: ultrasound, high-frequency, UV, skin exposure, exposure measurements.

The incidence of skin cancer is increasing in the U.S. and is attributed to the cumulative damage from repeated sunburns induced by the ultraviolet (UV) component of sunlight. While the link between cancer and sunlight is strong, the ability to predict any given individual's susceptibility to UV-induced skin damage is very limited. This study is a component of on-going work involving OST researchers to try to reduce that predictive uncertainty.

CDRH laboratories have used high-frequency (20 MHz) ultrasound imaging to measure changes in skin structure after exposure to UV radiation. Measurements were obtained on exposed and non-exposed areas of skin following a graduated series of known UV exposures. Ultrasound images were obtained immediately after exposure and at several time points during the healing interval. Initial data analysis found changes in the dermal thickness properties of the skin. A new phase of the study is being conducted and includes a larger number of subjects and data samples per subject. The results are promising but warrant further study. This work is part of a CDRH effort to find new approaches for evaluating the safety and efficacy of UV-emitting products regulated by FDA.

RADIATION METROLOGY

Radiation safety continues to be a significant concern for the Center. To help address this topic, OST 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 Mammography Quality Standards Act (MQSA). In addition, about 1,600 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. OST provides OC, OHIP, ORA, and Agreement States 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 OST provides 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, OST provides laboratory measurements and calibrations of light meters, laser measurement instrumentation, and microwave oven instruments for field enforcement of FDA performance standards. OST staff also provides pre- and post-market evaluations of selected products for compliance with FDA radiation standards.

The CDRH radiation measurement and calibration laboratories are internationally respected, and laboratory staff contribute significantly to the development of measurement protocols of new standards. For example, laboratory staff have been instrumental in establishing the national standard for mammography x-ray calibrations and continue to work closely with NIST. Additionally, staff have been closely involved in the effort to align the FDA Laser Standard with its international equivalents. The measurement and calibration program is a cost effective method of providing a large volume of high quality calibrations for a nationwide network of inspectors. FDA can be assured that compliance measurements are traceable to national standards. Traceability can be readily verified, because FDA is the sole custodian of the traceability chain. The laboratory's services are used for leveraging state agencies to test newly installed radiological equipment against FDA requirements, resulting in hundreds of additional inspections per year. The program allows both FDA and the states to avail themselves of traceable calibrations, which are independent of regulated industry, thus eliminating potential conflicts of interest.

Endoscope Hazard Evaluation

Key words: endoscopes, radiation, hazards

Work was initiated in FY 2000 to characterize the optical radiation emissions from endoscopes used in various minimally invasive diagnostic and therapeutic procedures. Data obtained from measurements of spectral radiant power showed that there is relatively little ultraviolet radiation emission below a wavelength of 370 nm and greatly attenuated emissions at wavelengths greater than about 700 nm.

In FY 2001, further tests were conducted of the spatial beam profiles from endoscopes. It was found that the spatial beam profiles from some of these devices is highly non-uniform, an unexpected result. A new test method was developed which uses a lens imaging beam profiler system to characterize non-uniform spatial profiles. In addition, a new field portable rapid scanning spectroradiometer system was obtained and characterized. This new system provides FDA with the capability of making rapid absolute spectral irradiance measurements under field conditions. These new measurement systems will be used in FY 2002 to complete a comprehensive evaluation of a wide variety of endoscopes. The data obtained in this work will be incorporated in reviewer guidance documents as a benchmark for evaluating the optical radiation safety of new devices and will provide the technical basis for setting safety limits to be included in international standards.

Ophthalmic Instruments Hazard Assessment

Key words: fundus cameras, radiation, hazards

Scientists started work in FY 2000 to determine the potential optical radiation hazards associated with the use of fundus cameras used to obtain photographs of the retina. Measurements were taken of the spectral integrated radiant exposure of the light emitted from pulsed Xenon light sources used in these devices. Preliminary data obtained showed relatively little ultraviolet and infrared radiation emissions from the device tested.

In order to evaluate the potential hazards to the retina, it is also necessary to characterize the spatial beam profile of the radiation on the retina. In FY 2001, a new test method to measure spatial beam profile was developed. The new test method uses a lens imaging beam profiler system. In addition, a new field portable rapid scanning spectroradiometer system to measure the pulsed light from fundus cameras was obtained and characterized.

This new system provides FDA with the capability of making absolute spectral radiant exposure measurements under field conditions. These new measurement systems will be used in FY 2002 to complete the hazard evaluation of fundus cameras. The data obtained in this work will be incorporated in reviewer guidance documents as a benchmark for evaluating the optical radiation safety of new devices, and will provide the technical basis for setting safety limits to be included in international standards.

Ophthalmic Instrument Standards

Key words: standards, ophthalmic instruments, intraocular lenses

OST scientists were active participants in developing major amendments to the ISO 15004 ophthalmic instrument standard. This standard is particularly important to CDRH since it will be applicable to all instruments that direct optical radiation into the eye. This includes medical devices and radiologic products utilizing lasers, pulsed light, operation microscopes, and endoilluminators. Some of these devices have produced retinal burns during ocular surgical procedures. It is expected that the final committee draft will be reviewed by the full ISO TC172 committee in early 2002.

OST is also active in developing voluntary standards for ophthalmic devices through participation on the ANSI Z80 subcommittees for optical engineering issues. In FY 2001, the OST representative to ANSI Z80.11 was appointed as co-chair of the working group and chair of the Technical subcommittee. In FY 2001, ANSI Z80.7 (Intraocular Lenses) was harmonized with the ISO 11979 series. The revised standard was circulated for vote in the early part of FY 2001 and was approved. There are three additional standards being developed in ANSI Z80. These are Z80.11 (Laser Systems for Corneal Reshaping), Z80.12 (Multifocal Intraocular Lenses), and Z80.13 (Phakic Intraocular Lenses). Z80.12 and Z80.13 have also been submitted to, and accepted by, ISO TC 172/SC 7 as New Work Items (NWIs). Work on the Z80.11 document will continue through FY 2002.

OST continues to assess test methods which are designed to confirm the optical properties (refractive power and resolution) of intraocular lenses (IOLs). In FY 2002, OST will also participate in developing a method for computer modeling optical performance, in a model eye, of intraocular lens designs.

Laser Field Compliance Program

Key words: lasers, calibrations, product testing, technical support

During FY 2001, OST continued to provide support to the laser field compliance program through consultations on optical radiation measurements. The OST Laser Calibration Laboratory maintains equipment for conducting high-precision optical measurements, which provide validity to measurements made in compliance testing programs nationwide. The laboratory measurement standard is a C-series calorimeter built by the National Institute of Standards and Technology (NIST). To assure the validity of measurements made by OST, periodic intercomparisons are conducted with NIST, and in-house quality assurance procedures are followed. During the later half of FY 2001, work commenced to convert the C-series calorimeter control system to one similar to that used by NIST.

Microwave Oven Leakage Instrument Calibration

Key words: microwave ovens, instrument calibration, precision calibration, microwave leakage, non-ionizing radiation

Twenty-five microwave leakage survey instruments were calibrated in OST's Electrophysics Branch calibration facility to provide an independent source of data supporting the enforcement of the Federal Microwave Oven Performance Standard (21 CFR 1030). The calibrations were based on precision calibrations transferred from the old EPB Precision Anechoic Chamber that has since been demolished. OST continued to design and specify instrument positioning equipment and a chamber fire system to convert an existing shielded room in the new OST laboratory into an anechoic calibration chamber for precision microwave instrument calibration.

Laser Performance Standard

Key words: lasers, standards, harmonization

FDA is in the process of amending the performance standard for laser products to bring it into closer harmonization with the international standards issued by the International Electrotechnical Commission (IEC) [IEC 60825-1 and IEC 60601-2-22]. OST is providing support to this effort through membership on the CDRH workgroup.

Standard for Personnel Security Screening Systems

Key words: security screening, x-ray

A current issue of concern to FDA is the use of ionizing radiation for the security screening of individuals. Several installations of x-ray security scanners are currently in operation in this country and many more are being considered following the attacks of September 11. FDA has regulatory jurisdiction over these devices. OST has led the effort to develop an ANSI/HPS consensus standard to address the radiation safety issues of this practice. In fiscal year 2001, the Task Group completed a proposed draft standard and submitted the draft to the ANSI/HPS N43 Committee for review and balloting.

X-ray Instrument Calibration

Key words: calibration, x-ray measurement, laboratory accreditation.

OST laboratories provide traceability to the national standards for all x-ray measurements related to enforcing FDA regulations, including those promulgated under the Mammography Quality Standards Act (MQSA) and the Radiation Control for Health and Safety Act (RCHSA). This program supplies the following: calibrated x-ray instruments for routine compliance programs and all related field supplies; support for special measurements needed such as measuring the ionizing radiation output from personnel security scanners, night vision devices, contaminated medical and consumer products, CT beam profiles, etc.; specifications and procurement of instrumentation; and technical experts for developing standards for radiation safety for non-medical uses of radiation. The laboratory is presently accredited for calibrating three classes of x-ray instruments in radiation fields typical of general radiography, mammography, and electronic product radiation.

X-ray measurement traceability is achieved by operating a secondary standard laboratory accredited by the National Voluntary Laboratory Accreditation Program (NVLAP). In fiscal year 2001, a total of 1,375 accredited calibrations of radiation-measuring instruments were performed by irradiation in known x-ray fields. In addition, 606 electrical instrument pre-calibrations and 122 calibrations of non-invasive kVp were performed. Since many state agencies perform FDA inspections and sometimes use their own equipment, states rely heavily on this CDRH calibration service. In FY 2001, 64% of the calibrations were for instruments owned by FDA, 29% for instruments owned by state agencies, and 5% for instruments owned by other federal agencies. A large percentage of the instruments

calibrated– 64%--were designated for testing compliance with the Radiation Control for Health and Safety Act of 1968 (RCHSA). Twenty-three percent of the instruments were designated for testing compliance with the Mammography Quality Standards Reauthorization Act of 1998 (MQSA), and five percent of the instrument calibrations were in support of the Nationwide Evaluation of X-ray Trends (NEXT).

OST keeps track of approximately 2,800 pieces of equipment at over 500 inspector stations throughout the country and U.S. territories, instrument usage and calibration data. As required by NVLAP, the laboratory this year has participated in a Proficiency Test administered by the National Institute of Standards and Technology (NIST), has undergone an internal audit of operating procedures and of the Quality System, and has been subject to a site inspection by NVLAP assessors. The laboratory complies with NIST Special Publication 812: *Criteria for the Operation of Federally Owned Secondary Calibration Laboratories (Ionizing Radiation);* NIST Handbook 150: *NVLAP Procedures and General Requirements;* and ISO Guide 25: *General Requirements for the Competence of Calibration and Testing Laboratories.*

The calibration program is a cost-effective method of providing a large volume of calibrations for a nationwide network of inspectors. Through this program, FDA and states can avail themselves of traceable calibrations that are independent of the regulated industry, thus eliminating potential conflicts of interest.

REUSE / STERILIZATION / DISINFECTION / INFECTIOUS DISEASE DIAGNOSTICS

FDA has traditionally not regulated reprocessing of single-use devices, but recently decided that regulation was necessary to assure the safety and efficacy of reprocessed medical devices. The OST Reuse Program is designed to address the issues of safety and efficacy associated with the reuse of devices that are intended as single-use devices (SUDs). Data and other information obtained in this OST research program have contributed to this policy and will help in the final formulation and implementation of regulations. The experience gained from this program will allow CDRH to understand the problems and ask the right questions related to SUD reprocessing. SUDs were intended by the original equipment manufacturer (OEM) to be discarded after single use and not to be reused on another patient. SUDs used in interventional cardiology and in gastrointestinal

procedures are obtained from Walter Reed Army Hospital and the Washington Hospital Center. Difficulties in cleaning these devices indicated unique problems with access to lumens and interstices that may contain blood and tissue. If the device cannot be cleaned, it cannot be reprocessed safely. Consequently, a potential hazard may exist if the device is reused on another patient. These lumens and interstices are narrow and opaque, and protocols to clean and validate cleaning are being developed. Cleaning and sterilization are safety issues. SUDs were also examined for performance (efficacy) and damage associated with use and cleaning. Because of concerns for laboratory personnel safety, the retrieved devices must be disinfected and cleaned prior to being handled and inspected. Some devices were examined after simulated reuse and reprocessing. A large collection of devices and models of these devices are available for further study. Interventional cardiology devices include many models of percutaneous transluminal coronary angioplasty catheters (PTCA) [balloon catheters], balloon inflators, electrophysiology catheters, various cardiac ablators, ultrasonic imaging catheters, angiography catheters, guiding catheters, revascularization catheters, and balloon catheters for wedge procedures. The gastrointestinal devices include various models of GI biopsy forceps and snares, devices for retrieving gallstones (balloons, snares, ERCP devices), and various GI catheters. Ensuring clean SUDs is complex as each device has its own specific cleaning needs.

Protocols for cleaning, sterilizing and evaluating performance of these devices are being developed in OST. These studies provide independent data to support review and regulatory decision-making related to the adequacy of reprocessing procedures for SUDs. This research is designed to uncover problems that a reprocessor firm may inadvertently confront while reprocessing SUDs and that CDRH needs to be aware of in regulating the practice of reprocessing SUDs. The use of simple techniques, reagents, and readily available equipment is emphasized so that the results are transferred to the actual reprocessing undertaken in hospitals and third party reprocessors. However, newer technologies are also being incorporated to understand important advancements that must be considered for managing risks in the future.

This OST research program has contributed independent data and information that is being used in compliance actions and in device approvals. The output from this research has already played a major role in formulating the CDRH policy for third party reprocessors and hospitals. All third party reprocessors had to submit PMA applications for reprocessing Class III devices by February 14, 2001, and submit

510K applications for other devices by August 14, 2001. Hospitals were to submit PMA or 510K applications by August 14. The OST research team is active in reviewing these documents and in developing standards for cleaning methods/validation and issues of sterilization. Most recent, the research team has provided training programs to communicate and share knowledge of the critical reuse issues so as to improve and enhance performance of ORA field inspectors.

CDRH continues to be actively involved with the regulatory evaluation of premarket applications for commercial in vitro diagnostic devices. A relatively recent and important component of this effort is the evaluation of premarket nucleic acid-based kits used to detect and identify infectious microorganisms. OST scientists in collaboration with ORA/WEAC participated in the International Laboratory Study on Chemical Disinfectants. This includes over 20 laboratories around the world in a round-robin (Ring Test) study to validate methods for disinfecting medical devices. The OST/ORA labs are the only United States participants. OST scientists perform laboratory research projects that involve utilizing equipment and methodologies associated with these devices, and this experience enables them to 1) participate effectively in the CDRH regulatory review of the devices, 2) make informed regulatory decisions concerning the safety and efficacy of the devices and procedures, and 3) efficiently standardize the associated methodology.

Peptide Nucleic Acid Probe Detection of Mutations in *Mycobacterium tuberculosis* Genes Associated with Drug Resistance

Key words: Mycobacterium tuberculosis, diagnostics, polymerase chain reaction, peptide nucleic acid, antibiotic, drug resistance.

Pulmonary tuberculosis is one of the most important, life-threatening bacterial diseases in the world. In recent years tuberculosis control efforts have been severely threatened by the emergence of potentially dangerous drug resistant strains of *Mycobacterium tuberculosis* (MTB). Many of the specific gene mutations that cause drug resistance in MTB are point mutations in known chromosomal genes. *In vitro* diagnostic devices that utilize new technology for the rapid detection of drug-resistant MTB strains are needed, since classical bacteriological methods are tedious and time consuming. OST scientists and collaborators from CBER are developing a PCR-peptide nucleic acid (PNA)-based ELISA as a diagnostic method for the rapid detection and identification of point mutations in genes

associated with isoniazid and rifampin resistance in MTB. PNA probes are the basis for a new technology for detecting mutant nucleic acids, including single-point mutations because they have high thermal stability, strong binding capacity, and high binding specificity.

Specific-point, mutation-containing sequences and wild-type sequences of cloned mycobacterial genes were PCR amplified, denatured, and hybridized with PNA probes bound to microplate wells. Using 15-base PNA probes, the experimental conditions suitable for detecting clinically relevant point mutations in the two MTB genes were established. Hybridization of PCR-amplified sequences that contained these point mutations with complementary mutation-specific PNAs resulted in significant increases in ELISA response compared to hybridization using wild type-specific PNAs. Conversely, PCR-amplified wild-type sequences hybridized much more efficiently with wild-type PNAs than with the mutation-specific PNAs. Using the MTB-cloned genes and PCR-PNA-ELISA format developed here, MTB sequences containing point mutations associated with drug resistance could be identified in less than 24 hours. The results of this research have been published in the journal *BioTechniques*. The laboratory experience gained from the project also enabled the investigators to make informed pre-market evaluations of commercial *in vitro* diagnostic devices used for detecting infectious microorganisms and to participate in developing molecular diagnostics-related biotechnology standards.

Microarray-Based *In vitro* Diagnostic Devices: Detection and Identification of Antibiotic Drug Resistant Strains of *Mycobacterium tuberculosis*

Key words: microarray, diagnostics, Mycobacterium tuberculosis, antibiotic, drug resistance.

Public health is threatened by the emergence of potentially deadly antibiotic-resistant mutant strains of *M. tuberculosis.* To facilitate diagnosis and appropriate treatment, faster and higher-throughput *in vitro* diagnostic devices are needed to detect mutations associated with *M. tuberculosis* drug resistance. The purpose of this OSCC-funded project is to evaluate the use of state-of-the-art microarray technology for the rapid and accurate detection and identification of numerous drug resistant strains of *M. tuberculosis.* OST scientists in collaboration with CBER, NCTR, and ORA investigators are studying device performance (e.g., analytical sensitivity, specificity, and repeatability), with a goal of standardizing the methodology. The knowledge and experience gained in this project will

be used in regulatory evaluation of premarket microarray-based *in vitro* diagnostic device applications submitted to the Center.

Product Safety/Disease Control and Prevention

Key words: Transmissible Spongiform Encephalopathies (TSEs), product safety, infection control, TSE risks

An OST scientist served as Chair of the CDRH TSE Working Group and as a key member of the FDA TSE Coordinating Committee. OST scientists are providing leadership and scientific expertise in Center/Agency programs to resolve numerous cross-cutting scientific and regulatory issues regarding TSEs that impact FDA-regulated products with broad implications for public health.

TSEs are chronic, degenerative, and uniformly fatal neurological disorders of animals and humans. Two of the human TSE diseases are classical Creutzfekit-Jakob Disease (CJD) and a new variant of CJD called vCJD. For CDRH, emphasis is on preventing human TSE transmission through medical devices containing or manufactured with bovine-derived materials, human tissue-based devices, use and reuse of surgical instruments, and assisting device manufacturers in developing diagnostic tests for these diseases.

Significant accomplishments in support of Center /Agency TSE initiative include the following:

- Established approaches to address CDRH-specific items in the FDA TSE Action Plan through deliberations of the CDRH TSE Working Group and appropriate Center staff;
- Developed the FDA "Proposed BSE Rule" which would make bovine and bovine materials from BSE-positive or BSE high-risk countries prohibited materials in the manufacture of FDA-regulated products;
- Developed a draft plan to maintain an updated database of products containing or manufactured using animal derived materials;
- Developed the BSE Contingency Plan, which outlines measures to be taken in the event of a potential case of BSE in the U.S. and participation in ORA satellite broadcast as outreach/education to the field and constituent communities;

- Prepared, jointly with CBER, a requested draft document for the CDRH Center Director on the risk of transmitting TSEs through medical devices and products with components of bovine origin;
- Prepared, through a joint CDRH/CBER.CDC Working Group, draft recommendations on the decontamination and sterilization of medical devices exposed to the CJD agent;
- Developed (with CBER) guidance for industry on preventive measures to reduce the possible risk of transmission of CJD and vCJD by human cells, tissues, and cellular and tissue-based products; and
- Educated Center/Agency staff and scientific communities using presentations and publications.

DEHP Safety Assessment

Key words: DEHP, risk assessment, medical devices, PVC

Patients undergoing various medical procedures can be exposed to di-(2-ethylhexyl)phthalate (DEHP), a compound used as a plasticizer for polyvinyl chloride (PVC) medical devices. Since exposure to DEHP results in the development of adverse effects in experimental animals, OST conducted a safety assessment (http://www.fda.gov/cdrh/ost/dehp-pvc.pdf) to determine the likelihood that patients exposed to this compound would experience similar effects. The results of the safety assessment suggest that children, especially male neonates, undergoing certain medical procedures may represent a population at increased risk for the adverse effects of DEHP. Based on the results of the safety assessment, CDRH issued a consumer update (http://www.fda.gov/cdrh/ocd/dehp.html#2) to inform the public and health care professionals of the potential risks posed by patient exposure to DEHP released from medical devices.

Studies on Reuse of Single-Use Devices

Key words: reuse, single-use devices, cleaning, disinfection, reprocessor, ethylene oxide, sterilization

In FY 2001, scientists continued to study the issues of cleaning medical devices to establish their safety and efficacy for reuse. A major part of the study addressed detecting and cleaning the lubricating oils from medical devices. A second major part of the study

addressed the use of disinfectants in cleaning processes. Disinfectants, other than bleach, make cleaning difficult and also provide some false information on cleaning strategies. These data have been used in formulating CDRH regulatory actions, establishing criteria for review of PMA's and 510K's, and providing methods for the Office of Compliance to inspect reprocessor firms. Scientists have completed studies of the amount of ethylene oxide, (a common sterilant) residues in medical devices placed under various experimental conditions, such as multiple exposures, differing extraction conditions, and differing extraction media.

Endotoxin-Mediated Potentiation of Toxicity: Implications for Reprocessing and Reuse

Key words: endotoxin, reuse, potentiation of toxicity, medical device materials, ISO 10993-17

Patients can be exposed to bacterial endotoxin following the use of improperly reprocessed medical equipment. Such exposures can have clinically significant consequences since endotoxin has been shown to potentiate the adverse effects of a number of chemical compounds that could be released from medical devices. In FY 2001, OST initiated laboratory studies to determine the extent to which endotoxin potentiates the toxicity of specific compounds released from devices. In addition, OST staff examined whether the approach described in ISO/DIS 10993-17 to set allowable limits for compounds released from devices is sufficient to protect critically ill patients from chemically induced adverse effects.

ELECTRONICS/ELECTRICAL ENGINEERING/SOFTWARE ENGINEERING/SYSTEM ENGINEERING

Electronic, software, and systems engineering concerns lie at the heart of the problems encountered with most of the sophisticated new medical devices regulated by the Agency. A critical core of expertise has been developed in each of these areas to address Center needs.

The DECS program provides a broad range of technical assistance in these areas to ORA and to all Center components. In addition, it includes active efforts in

standards development, tool development and monitoring, demonstration projects, and training/industry outreach. Engineers in this program investigate and analyze issues involving the design of complex medical devices, focusing on both the adequacy of designs themselves and on the adequacy of the manufacturer's design and manufacturing processes.

In the premarket area, DECS engineers review and analyze information submitted by the manufacturer, including product descriptions, design documentation, and engineering data, to determine whether the firm's engineering and clinical judgments concerning safety and effectiveness are reasonable. DECS engineers participate in plant inspections when their specialized expertise is requested by ORA. They review and analyze information submitted by the manufacturer, including quality manuals, procedures, work instructions, and records, to assess the degree to which the manufacturer's quality system conforms to FDA requirements and the degree to which a quality system is being followed in practice. They also plan and execute special laboratory investigations in order to either confirm a performance claim made by a manufacturer or to determine the root cause of a medical device failure.

Electronics/Electrical Engineering in Medical Devices

Key words: electrical engineering, electronics

OST provides technical support for issues involving the use of electronics in medical devices. The areas of specific concentration include the following:

- Sensors, Analog and Digital Signal Processing, Data Acquisition
- Microprocessor and Digital System Design
- Batteries, Power Electronics, Power Quality
- MEMS Devices, Microcircuits
- Electrical Safety, Fire Safety
- Electronic Design and Manufacturing Processes

The support that OST provides in this area of consists of the following:

- Policy Interpretation and Implementation
- Technical Assistance to ORA/OC/ODE

- Standards Development and Insertion
- Tools Development/Monitoring of New Tools
- Demonstration Projects
- Training/Industry Outreach.

Engineers in this program area investigate and analyze issues involving the design of electronic medical devices, focusing on both the adequacy of the designs themselves and on the adequacy of the manufacturer's design and manufacturing processes.

In the premarket area, OST engineers review and analyze information submitted by the manufacturer, including product descriptions, design documentation, and engineering data, to determine whether the firm's engineering and clinical judgments concerning safety and effectiveness are reasonable. In FY 2001, OST engineers performed 37 engineering reviews of premarket submissions.

In support of FDA field enforcement activities, OST engineers participate in plant inspections when their specialized expertise is requested by ORA. They review and analyze information submitted by the manufacturer, including quality manuals, procedures, work instructions, and records, to assess the degree to which the manufacturer's quality system conforms to FDA requirements and the degree to which to a quality system is being followed in practice. They also plan and execute special laboratory investigations, in support of regulatory activities, in order to either confirm a performance claim made by a manufacturer or to determine the root cause of a medical device failure. In FY 2001, OST engineers performed substantive analysis and/or investigations in 10 compliance cases.

OST engineers develop laboratory test methods to facilitate the regulatory review process. They accomplish this by providing objective and repeatable approaches to measuring aspects of device performance that bear on safety and/or effectiveness in addition to developing custom instrumentation to support other FDA internal research activities.

OST engineers consult with other government agencies, standards-setting organizations, university researchers, and professional societies on matters related to the design and manufacturer of medical electronics.

OST staff members are involved in an ongoing project to upgrade the instrumentation in the CDRH X-ray calibration laboratory. They have developed a new architecture, involving a network of microprocessor-based controllers, which has significant reliability

and performance advantages over the existing system. In FY 2001, the operation of the first of the new controllers was validated.

Software Use in Medical Devices

Key words: software, software safety, software engineering

OST provides technical support for issues involving the use of software in medical devices. The discipline of software engineering includes the following four broad areas:

- software safety and software risk management;
- software requirements, analysis, and definitions;
- software design methods; and
- software verification, validation, and testing.

The support that OST provides in the area of software engineering consists of the following:

- policy interpretation and implementation;
- technical assistance to ORA/OC/ODE;
- standards development and insertion;
- tools development/monitoring of new tools;
- demonstration projects; and
- training/industry outreach.

Engineers in this program area investigate and analyze issues involving the design of software use in or as medical devices, focusing both on the adequacy of designs themselves and also on the adequacy of the manufacturer's design processes. They review and analyze information submitted by the manufacturer, including product descriptions, specifications and requirements, design documentation, hazard analysis, and verification, validation and testing information, to assess the safety and effectiveness of the software. In FY 2001, OST engineers performed 103 software reviews of premarket submissions.

In support of enforcement activities, engineers in this program area participate in plant inspections when their specialized software engineering expertise is requested by ORA. In this role, they act as national software experts for ORA. They also review and analyze information submitted by the manufacturer, including quality manuals, procedures, and

records, to assess the degree to which the manufacturer's quality system conforms to FDA requirements, and the degree to which to a quality system is being followed in practice. OST software engineers have provided extensive support to other FDA Centers (for example, helping CBER to manage complex issues involving blood bank software by reviewing seven premarket application in FY 2001).

OST engineers develop laboratory projects to evaluate tools that can be used to facilitate the regulatory review process by providing objective and repeatable approaches to measuring aspects of software performance that bear on safety and/or effectiveness. They are also working with Agency senior staff to develop policy related to Part 11 - Electronic Records and Signatures.

OST engineers consult with other government agencies, standards-setting organizations, university researchers, and professional societies on matters related to the design and manufacturer of medical electronics. OST engineers conduct outreach programs to help regulated industry and academia understand FDA policy related to software.

An OST software engineer represents FDA on both the DARPA High-Confidence System Workgroup and the National Science Foundation's High-Confidence Software and Systems initiative. These government-wide groups fund the research of engineering methods for safer, more secure and more reliable software. FDA provides public health concerns in this forum. This engineering input fosters improvement in the state-of-the-software-art, which provides medical device manufacturers with the tools necessary to produce safe and effective software.

Medical Device Systems

Key words: quality systems, risk management, reliability, systems engineering

Medical devices that incorporate electronics and/or software are inherently complex devices. Engineers who develop and analyze these devices must be able to skillfully peel back many layers of abstraction from the underlying mathematical models that govern device operation, to their hardware and software realizations, and down to the physical characteristics of component parts.

Historically, many device problems arise at the intersections of hardware and software, the user, the manufacturing process and the use environment. A broad range of analytical tools

are available to systems engineering specialists to help them identify such problems and take reasonable steps to prevent or limit the problems and/or mitigate the consequences.

Different analytical techniques are applicable at different stages of the device life cycle. These techniques permit systems engineers to manage the complexity of the design by providing a structured approach to dealing with different aspects of the design. The term *system effectiveness* has been used in industry to describe the range of concerns addressed by these analytical techniques, including the following:

- reliability
- dependability
- maintainability
- manufacturability
- testability
- serviceability
- capability
- safety engineering and risk management
- metrology

OST engineers have extensive practical experience in all of these areas of concern. In the area of reliability engineering, for example, expertise exists in the analytical techniques used to characterize system reliability. There is also expertise in component-level failure modes and control methods. For example, OST investigated damage due to electrostatic discharge in semiconductors and integrated circuits and failures of multilayer ceramic packages due to metal migration through microscopic cracks in the ceramic dielectric material.

In the area of electronic packaging, OST addressed issues of thermal management and susceptibility of circuits to environmental influences such as temperature and humidity extremes, water and chemical ingress, shock and vibration, and radiation.

Due to the enormous breadth of technologies employed in medical devices, it is impossible to cover all of these areas in depth. Instead, OST focuses on understanding the principles of system effectiveness. In many cases, OST relies heavily on external subject matter experts from industry, academia, and other Government laboratories, particularly, NASA, NIST, and the Department of Energy National Laboratories. OST's role is to analyze the device issue in order to understand the nature of the problem, seek out the appropriate

technical expertise, and interpret the information obtained in the context of the clinical application and the FDA regulatory environment.

With the implementation of the Total Product Life Cycle (TPLC) approach to regulating medical devices, the concept of system effectiveness takes on a whole new and significantly more meaningful role for the Center. OST engineers have long advocated a TPLC approach to medical device design. In recent years, OST's systems engineering approaches have been applied to numerous CDRH internal regulatory processes through invited participation in re-engineering teams and related management initiatives.

OST provided consultation to various field investigators on a variety of quality system issues involving design controls, corrective and preventive actions, and calibration of test and measuring equipment. The focus of OST's contribution in these cases is reconciling the general requirements of the quality system regulation with the specific practices of the electronics industry.

STATISTICAL ISSUES OF DIAGNOSTIC MODALITIES

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

The methodological tools being developed for analyzing the performance of imaging systems within the context of reader variability are referred to broadly as the multiple-reader, multiple-case (MRMC) receiver operating characteristic (ROC) paradigm. The paradigm is a multivariate analysis of the map of reader true-positive rates versus false-positive rates as a function of the variables listed above. A key question OST scientists are investigating is that of analyzing not only reader or system average performance but also the multivariate uncertainties that result from the finite sample of patients and readers.

The approach to the assessment of systems for computer-aided diagnosis and high-dimensional DNA arrays is an extension and application of the multivariate approach to ROC analysis. In the case of CADx and DNA arrays, the key question is that of analyzing the multivariate uncertainties that result from the finite sample of patients used to train the system, the finite sample of patients used to test the system and their interaction. The general subject of uncertainty analysis also addresses the classical problem of the "generalizability" of performance of a CADx or micro-array algorithm. OST makes use of advanced statistical tools for diagnostic decision-making under uncertainty, including classical Bayes' discriminants, neural-network architectures, and fuzzy logic, in studies of CAD algorithms and their performance.

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

Software Development for Multivariate ROC Assessment of Diagnostic Modalities and Systems for Computer-Aided Diagnosis

Key words: computer-aided diagnosis, clinical trial design

This program addresses the development of analytical methodology and software for assessing diagnostic imaging modalities and systems for computer-aided diagnosis in the presence of multiple random effects (patient cases, image readers, and multiple correlations). OST scientists have previously developed methods and software for the efficient design and sizing of clinical trials within this paradigm in imaging. OST has now extended this work to include the effects of the finite sample sizes used for training and testing in the development of algorithms for computer-aided lesion detection and classification. This work is immediately relevant to the design and sizing of databases for use by industry sponsors of such systems and public-policy-making bodies such as the National Cancer Institute and the FDA, who either sponsor such databases (NCI) or may depend on them as part of submissions from industry sponsors of such computer algorithms (FDA).

Tissue Characterization

Key words: ultrasound, magnetic resonance imaging, spectroscopy, tissue characterization

This project involves applying quantitative methods for tissue characterization using ultrasound and magnetic resonance. An understanding of the physics of these modalities and the statistical issues involved in multi-parameter tissue characterization is important in reviewing diagnostic devices. OST continued to participate with the American Institute of Ultrasound in Medicine Technical Standards Committee Working Group on Backscatter Measurements to develop a standard for ultrasonic backscatter measurements in tissue. OST continued to participate in developing the ASTM "Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants." This standard was voted on and approved recently and is now an official ASTM standard. Researchers are still collecting ultrasound and pathology data from *ex vivo* prostates at the University of Vermont to assess the usefulness of combining clinical, sonographic, and elastographic features to improve the detection of prostate cancer. Software was developed to compute backscatter coefficient, texture, and elastographic parameters from prostate samples.

The Medical Image Perception Conference IX (MIPC IX)

Key words: medical imaging, radiologists, assessment methodology

The ninth biennial conference on Medical Image Perception was held at the Airlie Conference Center in Warrenton, VA from September 20-23, 2001. This conference was organized by researchers in OST's Division of Electronics and Computer Science. Over 80 conferees and speakers came from 6 European countries and the United States. The topics of the conference were reader strategies, variability, and error in diagnostic imaging; statistical assessment methodologies; model observers and image quality assessment; computer-aided diagnosis; and problems in medical image display. There were invited tutorials, proffered papers, and workshops for each topic. Representatives from CDRH, the National Cancer Institute, the American College of Radiology Imaging Network (ACRIN), academia, and industry provided state-of-the-art science and methodology that is useful for the process of consensus discovery and the development of FDA guidance for industry submissions in these areas of diagnostic medicine.

Factors That Affect the Performance of Self-Monitoring Glucose Meters

Key words: glucose, diabetes

Results from this project revealed that operator variability, meter precision, and inter-meter difference were minor contributors to the inaccuracy of blood glucose meters. The main factor appeared to be systematic errors in the meter calibration. Meter strip lot-to-lot variation was found to be up to ±10% for the four meters. The 14 test assay kits from the hexokinase comparative method had 0.2 to 4.8% deviation from the true glucose values certified for NIST's standard SRM sera.

These findings have provided the FDA first hand independent information to support better guidelines for the manufacturers' submissions and also provide reliable information regarding the performance limits of the glucose meters.

WIRELESS TECHNOLOGIES

The wireless technology revolution, together with a flood of new medical devices incorporating sensitive microelectronics, is leading to a highly unstable situation. Dangerous malfunctions can be induced in devices via electromagnetic interference

(EMI) from wireless equipment, such as cellular phones and magnetic-field emitting security devices.

OST's Division of Physical Sciences (DPS) is currently collaborating with the Federal Aviation Administration (FAA) on an investigation of the potential interaction between metal detectors and implanted medical devices, such as spinal and deep brain stimulators. This effort includes mapping electromagnetic fields emitted from security-screening systems, developing a simulator for testing medical devices for interference, and testing high-risk medical devices for susceptibility to EMI.

DPS has also responded to concerns about the radiation from handheld wireless (cellular) telephones by developing a cellular telephone measurement standard in conjunction with the IEEE. A well-defined measurement standard is necessary if both manufacturers and regulatory agencies are to have confidence in the measurements they make. To further this effort, OST developed standardized methods to measure the absorption of radiation in a human head model.

In addition to laboratory work, DPS routinely performs regulatory reviews of premarket submissions and post-market assessments of EMI, including 1) devices affected by EMI (implanted and external cardiac stimulation devices, powered wheelchairs and scooters); devices that can interfere with other medical devices (benign prostatic hyperplasia and cancer hyperthermia devices; and 3) MRI systems whose pulsed radio-frequency fields cause heating of metallic implants. In addition, DPS is developing labeling for 1) implanted medical devices to warn of heating that led to the deaths of two individuals in the past year. (These patients were inappropriately treated with radio-frequency diathermy, since they had metallic leads implanted in their central nervous system.); 2) electronic anti-theft security systems to avoid injuries to users of implantable medical devices; and 3) implanted nerve stimulation devices to avoid patient injuries from exposure to magnetic fields by security systems.

DPS also participates in numerous standards-setting activities, including 1) standards for EMI of implanted cardiac stimulation devices from wireless handheld phones and magnetic field-emitting security systems; 2) recommended practices for ad hoc EMI testing of medical devices with portable radio transmitters; 3) an international consensus standard for powered wheelchairs; 4) a measurement standard for microwave absorption from handheld wireless (cellular) telephones;

and 5) a national consensus standards for hearing aid electromagnetic compatibility (EMC) with cellular telephones. In addition, DPS is participating in the development of an international draft position paper on harmful EMI effects to medical devices from security systems. This draft document was prepared by a working group sponsored by the International Commission on Non-Ionizing Radiation Protection (ICNIRP).

Evaluation of Quality Assurance Standard for the Measurement of Cellular Telephone Specific Absorption Rate

Key words: cellular telephone, specific absorption rate, wireless, dosimetry, microwave

This project is being performed in support of an emerging standard being promulgated by the Institute of Electrical and Electronic Engineers. The voluntary standard is entitled "Recommended Practice for Determining the Spatial-Peak Specific Absorption Rate (SAR) in the Human Body Due to Wireless Communications Devices: Experimental Techniques." It sets forth the first consistent test methodology for measuring (dosimetry) the Specific Absorption Rate (SAR) induced in the human body by cellular telephones and wireless handsets that emit microwave radiation. The lack of a standardized test methodology has lead to widely varying results when the SAR induced by the same wireless device is measured at different laboratories with different simulated human head models. The inability to produce consistent results by different labs has caused consumer distrust, recalls, and regulatory confusion. In FY 2001, OST engineers developed and built an SAR measurement lab consisting of a data-acquisition system and three-dimensional, full-motion scanner to perform these tests. Then, in collaboration with the University of Maryland, they developed an SAR quality assurance (QA) system consisting of a simple model of a simulated wireless handset and human body phantom. This QA system will be circulated next year to many international labs to perform intercomparisons of SAR measurements.

Wireless Medical Telemetry

Key words: wireless medical telemetry, electromagnetic interference (EMI), Wireless Medical Telemetry Services (WMTS), Federal Communications Commission (FCC),

During FY 2001, OST continued to work in partnership with the Federal Communications Commission (FCC), the American Hospital Association (AHA), telemetry manufacturers, and clinicians to help the FCC further refine and defend the use rules for the dedicated

frequency bands of the new Wireless Medical Telemetry Services (WMTS). The WMTS provides unique protections against EMI and reduces the risk of interference to wireless medical telemetry from other in-band radio sources. This work addresses public health risks to wireless medical telemetry and positions the Center to focus on the correct areas for regulatory decisions.

Laboratory Testing of Cardiac and Electrical Stimulation Devices
Key words: electromagnetic interference (EMI), electromagnetic compatibility (EMC), electrical stimulation devices, nerve stimulation devices, cardiac stimulation devices, cellular telephone, metal detectors, wireless handset

This project is intended to assess the electromagnetic compatibility (EMC) of several high-priority ambulatory and implanted electrical stimulation medical devices. OST collaborated with personnel from ODE and OSB in a CDRH ad hoc group. This group identified over 20 reports of EMI of implanted neural stimulators that caused patient injuries. These reports included EMI from a variety of magnetic-field-emitting security systems. After identifying problematic devices, the Electrophysics Branch labs in OST continued to study potential interference of implanted and ambulatory medical devices by electromagnetic fields emitted from security systems. This work was performed in the EPB labs with support from the Federal Aviation Administration (FAA) under an interagency agreement between the FDA and FAA.

The OST laboratories also performed experiments to assess deep brain stimulators (DBS). This was done in response to clinical reports of serious patient injuries (including two deaths) from interactions with electromagnetic fields applied to the patients by radio frequency diathermy. These studies provided independent data supporting regulatory decisions that CDRH had to make regarding safety alerts about use of diathermy in patients with a DBS.

Development of a Standardized Test Method for Evaluating Interference from Electronic Security Systems

Key words: electromagnetic compatibility, EMC, interference, electromagnetic interference, EMI, metal detector, electronic surveillance system, cardiac pacemaker,

This project involves evaluating implantable medical devices for their susceptibility to electromagnetic interference (EMI) from electronic article surveillance systems (EASS), metal detectors and other security systems that emit low-frequency magnetic fields. EASS are used in many retail stores to prevent shoplifting by detecting special tags placed on merchandise. Security systems such as metal detectors are used to screen people for metal objects that can be used as weapons. The goal of this project is to develop a standardized laboratory test method to check the susceptibility of implanted medical devices with the magnetic fields emitted by these security systems. There is great similarity between EASS and metal detectors, in terms of the magnetic field exposures they produce for patients with medical devices implanted in their bodies. Magnetic field emissions from six different walk-through metal detectors were measured in detail. This project is closely associated with the OST project "Laboratory Testing of Cardiac and Electrical Stimulation Devices." The project also supports the work specified in the FDA interagency agreement with the Federal Aviation Administration for evaluating medical device EMI from emissions of airport security systems (metal detectors).

APPENDIX A – OST Publications

October 1, 2000 – September 30, 2001

Journal Articles

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APPENDIX B – OST Presentations

October 1, 2000 – September 30, 2001

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Anderson LE, Morris JE, Sasser LB, Creim JA, Desta AB, Cress LW, Owen RD. An evaluation of ornithine decarboxylase activity in brain regions of fetal rats exposed to radiofrequency fields. Annual Meeting of the Bioelectromagnetics Society, St. Paul, Minnesota, June 2001.

Badano A. Workshop on evaluating the multivariate display image quality: interplay of display artifacts. Medical Image Perception Conference IX, Warrenton, VA, September 2001.

Badano A, Kim J, Kanicki, J. Optimal color for supra-threshold and threshold contrast perception. Medical Image Perception Conference IX, Warrenton, VA, September 2001.

Bassen HI. Interference of magnetic field emitting systems with active implanted medical devices (AIMD). Workshop on the Health Impact of Electromagnetic Fields of the Fifth Framework Programe of the EC Federal Office for Radiation Protection, Munich, Germany, March 19, 2001.

Bassen HI, Witters DM. Electromagnetic interference with medical devices. TATRC, Ft. Detrick, Frederick, MD, February 22, 2001.

Beer JZ, Bushar HF, Busick DN, Chwirut DJ, Cyr WH, Ediger MN, Lao NT, Matchette LS, Miller SA, Lopez H, Weininger S, Zmudzka BZ, Toombs E, Jorgensen H, Korossy KS, Hearing VJ, Kobayashi N, Tadokoro T, van der Leun JC, Lenderink E. Studies on parameters of UV response in human skin: a progress report. FDA Science Forum, Washington, DC, February 15-16, 2001.

Beer JZ, Miller SA, Lao NT, Zmudzka BZ. Production and persistence of UV-induced tan. Biologic Effects of Light Symposia - 2001, Boston, MA, June 15-17, 2001.

Beer JZ. Predicting sensitivity to UV radiation - needs and approaches. 28th Annual Meeting of the American Society for Photobiology, Chicago, IL, July 7-12, 2001.

Beiden SV, Wagner RF, Campbell G, Metz CE, ChanH-P, Nishikawa RM, Schnall MD, Jiang Y. Analysis of components of variance in multiple-reader studies of computer-aided diagnosis with different tasks. SPIE Conference "Medical Imaging 2001," San Diego, CA, February 17-23, 2001.

Byrnes GA, Miller SA, Mazur DO, Grossman LW. Laser characteristics through fundus contact treatment lenses: risk potential for anterior segment complications. FDA Science Forum, Washington, DC, February 15-16, 2001.

Cerra F. Status of a draft standard for personnel security screening systems. 34th Midyear Topical Meeting of the Health Physics Society, Madison, WI, February 2001.

Chen ET, Nichols J, Duh S-H, Hortin G, Gonzalez-Licea A. A study of the factors that affect the performance of the blood glucose monitoring devices. AACC Annual National Meeting, Chicago, IL, July 28-August 2, 2001.

Chenault VM, Pugliese CE, Garner FM. The extraordinary pathology seen in *Psammomys obesus* (Sand rat): what's your diagnosis? National Capital Area/ American Association for Laboratory Animal Sciences. Computer Presentation/Poster Session. October 2000.

Chenault VM (invited speaker), Carter ER, King JF, Ansari RR. Non-invasive detection of ocular changes and cataracts in *Psammomys obesus* (Sand rat). Third Asian Cataract Research Conference, Hong Kong, China , November 2000.

Chenault VM, Ediger MN, King JF, Ansari RR. Dynamic light scattering from space to earth: looking at diabetes through the eye. Inaugural Event USUHS Interdepartmental Center for Space Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD, November 2000.

Chenault VM. Technology transfer from space to earth: helping diabetes. Innovations in Government (website).

Chenault VM, Ediger MN, Ansari RN (NASA). Unusual animal models: Psammomys obesus. 10th International Laser Physics Workshop, Moscow, Russia, July 2-7, 2001.

Chenault VM. Overview of FDA and sand rat diabetes research. Class for Bridges Student Program, Virginia State University, Petersburg, VA, April 20, 2001.

Chenault VM. Overview of FDA and CDRH's role in regulatory decision: public health is everybody's business. University of Houston graduate colloquium, Houston, TX, August 20, 2001.

Chenault VM. Use of the sand rat for the study of the ocular complications of diabetes. Woods Hole Marine Biology Laboratory, Woods Hole, MA, August 24, 2001.

Cyr WH. Update on regulatory activities on sunlamps and sunbeds. Federal Council on Skin Cancer Prevention, Washington, DC, June 9, 2001.

Cyr WH. Recommended exposure schedules for sunlamps and tanning beds: past, present and future. Book of Abstracts for the American Society for Photobiology, Chicago, IL, July 8, 2001.

Das SS, Schroeder LW. Basis for constructing an accelerated methodology for determining the shelf life of latex medical gloves. FDA Science Forum, Washington, DC, February 15-16, 2001.

Elespuru RK. Development of an *in vitro* mutagenicity assay. International Agency for Research on Cancer, Lyon, France, July 11, 2001.

Faaland RW, Grossman LW. Design and evaluation of a null lens for testing the optical performance of silicone intraocular lenses. FDA Science Forum, Washington, DC, February 15–16, 2001.

Faaland RW, Grossman LW. Design and evaluation of a null lens for testing the optical performance of silicone intraocular lenses. Annual Meeting of the Commissioned Officers Association of the USPHS, Washington, DC, May 29–31, 2001.

Gagne RM, Quinn PW, Myers KJ, Doyle R. (Poster) Optically coupled digital radiography: sources of inefficiency. FDA Science Forum, Washington, DC, February 2001.

Godar DE. UV doses of American children and adolescents. 29th Annual Meeting of the American Society for Photobiology, Chicago, July 7-12, 2001.

Hilbert SL, Boerboom LE, Livesey SA, Ferrans VJ. A morphologic study of explanted decellularized carotid artery vascular grafts. Proceedings of the Workshop on Engineering Tissues, Hilton Head Island, SC, p 12, February 21-25, 2001.

Hitchins VM (speaker), Mtungwa AR, Brown SA, Merritt K. Induction of TNF-alpha, IL-1 beta, IL-6, and nitric oxide (NO) by titanium alloy particles (TiAlV) and LPS in RAW 264.7 murine macrophage cells. Presented at the Annual Meeting of the Society for Biomaterials, St. Paul, MN, April 24-29, 2001.

Hitchins VM (speaker), Mtungwa AR, Merritt K, Whitby JL. Detection of lipopolysaccharide and lipoteichoic acid by measuring nitric oxide production in RAW 264.7 murine macrophage cells. Presented at the Annual Meeting of the Society for Biomaterials, St. Paul, MN, April 24-29, 2001.

Hitchins VM, Mtungwa AR, Merritt K. Induction of TNF-alpha, IL-1beta, IL-6, and nitric oxide by lipopolysaccharide in combination with titanium alloy particles in RAW 264.7 murine macrophage cells. Gordon Research Conference on Biomaterials: Biocompatibility and Tissue Engineering, Holderness, NH, July 22-26, 2001.

Hutter JC, Long MC, Richardson DC, Luu HMD, Schroeder LW. A Monte Carlo simulation of the degradation of cellulose acetate hemodialysis membranes. American Chemical Society, 220th Annual Meeting, Chicago IL, August 26-30, 2001.

Hutter JC, Long MC, Schroeder LW. Modeling the degradation of common hemodialysis membrane materials. ACS National Meeting, Chicago, IL, August 26-30, 2001.

Ilev IK, Waynant RW, Bonaguidi MA. Evanescent wave delivery to a precise tissue area using fiber-optic tips. Photonics West–BiOS 2001 International Conference, San Jose, CA, January 20-26, 2001.

Ilev IK, Waynant RW. A high-resolution fiber-optic confocal microscope. Photonics West–BiOS 2001 International Conference, San Jose, CA, January 20-26, 2001.

Ilev IK, Waynant RW, Ediger MN. All-optical-waveguide ultraviolet (266 nm) laser delivery using a simple grazing-incidence-based hollow taper. International Conference on Lasers and Electro-Optics (CLEO-2001), Baltimore, MD, May 7-12, 2001.

Ilev IK, Waynant RW, Reiter M. A target-activated all optical fiber technique for on-off laser delivery into a precise tissue area. International Conference on Lasers and Electro-Optics (CLEO-2001), Baltimore, MD, May 7-12, 2001.

Ilev IK, Waynant RW. Optical sensing and imaging in biomedicine. Uniformed Services University of the Health Sciences, Bethesda, MD, June 7, 2001.

Ilev IK, Waynant RW. On-the-spot laser therapy using a smart, tissue-activated fiber probe. SPIE Conference on Nanostructure Science, Metrology and Technology, National Institute of Standards and Technology, Gaithersburg, MD, September 5-7, 2001.

Ilev IK, Waynant RW, Luedtke R. Fundamental optical techniques for non-invasive glucose monitoring. CDRH Meeting on Glucose Monitoring, Rockville, MD, September 18, 2001.

Kaplan DS, Picciolo GL, Garcia A, Burg K. Elements of a test method for cell adhesion assays for tissue engineering. Biomaterials-Tissue Engineering Gordon Research Conference, Holderness, NH, July 22-27, 2001.

Krauthamer V, Crosheck T. Rapid-rate nerve stimulation in computer modeled and real neurons. USPHS Commissioned Officers Association, Public Health in the 21st Century, Scientist Topics, Washington, DC, p. 47-48, May 28, 2001.

Lao NT, Zhoul SY, Borders RA. Headspace gas analysis of residual ethylene oxide in sterilized medical devices material - plasticized polyvinyl chloride and high density. AAMI Conference Expo 2002, Minneapolis, MN, June 1-4, 2002.

Lee SJ, Badano A., Hong Y, Kanicki J. Monte Carlo simulation of spectral photon emission of the organic polymer light-emitting devices. International Conference on Electroluminescence of Organic and Related Materials. UCLA, Los Angeles, CA, September 5-8, 2001.

Luu HMD, Kim C, Hutter JC. Physiologically based modeling of the endocrine disruption potential of bisphenol A in rats and humans. Society of Toxicology Annual Meeting, San Francisco, CA, March 2001.

Lyle DB, Bushar GS, Langone JJ. Screening biomaterials for complement activating potential. Proceedings of the 27th Annual Meeting of the Society for Biomaterials, St. Paul, MN, abstract p. 391, April 24-29, 2001.

Maish M, Hong T, Krueger PL, Stearns G, Gusafson E, Harper III J, Hoffman-Kim D, Hilbert SL, Hopkins R. An animal model for the evaluation of valve conduits: a comparison of cryopreserved sheep pulmonary valve allografts and human. American College of Surgeons, New Orleans, LA, 2001.

Malinauskas R. *In vitro* blood damage testing of medical devices - an FDA perspective. Workshop on Blood Trauma in Medical Devices, University of Pittsburgh, Pittsburgh, PA, September 14, 2001.

Maloof MA, Beiden SV, Wagner RF. Analysis of competing classifiers in terms of components of variance of ROC summary accuracy measures: generalization to a population of trainers and a population of testers. Medical Image Perception Conference IX, Warrenton, VA, September 20-23, 2001.

Matchette LS, Lenderink E, Zmudzka BZ, Miller SA, Beer JZ. Attenuation at 670 nm as a predictor of UV sensitivity. 28th Annual Meeting of the American Society for Photobiology, Chicago, IL, July 7-12, 2001.

Midgette W. Medical device risk management and the implementation of ISO 14971. American Society of Quality, San Francisco Biomedical Discussion Group Meeting, San Jose, CA, February 27, 2001

Midgette W. The implementation of ISO 14971 at the FDA. AAMI/FDA International Conference on Medical Device Standards and Regulation, McLean, VA, June 28, 2001.

Miller SA, Lao NT, Zmudzka BZ, Beer JZ. Evaluation of UV-induced tan vs. time – considerations for development of exposure schedules. 28th Annual Meeting of the American Society for Photobiology, Chicago, IL, July 7-12, 2001.

Myers KJ, Wagner RF. (Program Co-chairs and Editors). Medical Image Perception Conference IX. (A conference sponsored by the Medical Image Perception Society.) Program and Conference Abstract Book, Warrenton, VA, September 20-23, 2001.

Owen RD. EMFs and cancer - update on biological research. International Seminar on Electromagnetic Field Safety, World Health Organization and International Commission on Non-Ionizing Radiation Protection, Lima, Peru, March 8, 2001.

Owen RD. Wireless phones: focus on radiofrequency radiation and health. 57th Annual Educational Conference, Michigan Environmental Health Association, Lansing, MI, March 14-16, 2001.

Owen RD. Wireless phones. Annual Meeting of the Technical Electronic Product Radiation Safety Standards Committee (A U.S. Federal advisory committee), Rockville, MD, May 17, 2001.

Pfefer TJ. Minimally invasive optical diagnostics research in the FDA Office of Science and Technology. Uniformed Services University of the Health Sciences, Bethesda, MD, June 7,2001.

Pfefer TJ, Ediger MN, Schomacker KT, Nishioka NS. The influence of multi-fiber probe design on light propagation during fluorescence spectroscopy. United Engineering Foundation Conference on Advances in Optics for Biotechnology, Medicine and Surgery, Banff, Alberta, Canada, July 22-27, 2001.

Regnault WF. Scientific testing of biomaterials and medical devices, expectations, performance, reliability: the road to approval. Biomedical Engineering Materials and Applications (BEMA) Roundtable, Division on Engineering and Physical Sciences (DEPS), National Materials Advisory Board, National Research Council, Washington, DC, June 11, 2001.

Rinaldi J. Guidelines and lessons learned for creating a successful IDE application: device description and design specifications. ASAIO (American Society of Artificial Internal Organs) 47th Annual Conference, New York, NY, June 2, 2001.

Sams RL, Couch LH, Miller BJ, Okerberg CV, Beer JZ, Wamer WG, Howard PC. Acute and sub-chronic effects of co-treatment of female SKH-1 mice with alpha- and beta-hydroxyacids and/or simulated solar light. 28th Annual Meeting of the American Society for Photobiology, Chicago, IL, July 7-12, 2001.

Shope TB. Digital imaging systems: regulatory issues. 18th Annual Meeting and Workshops of the American College of Medical Physics, Hershey, PA, June 2-7, 2001.

Shope TB. Current activities to reduce radiation risks from interventional radiology. 33rd Annual National Conference on Radiation Control, sponsored by the Conference of Radiation Control Program Directors, Anchorage, AK, April 29-May 2, 2001.

Shope TB. Fluoroscopic x-ray equipment, interventional procedures and computed tomography. FDA/ORA Central Region Radiological Health Partnership Meeting, Baltimore, MD, August 15, 2001.

Silberberg JL. A regulatory perspective on the second edition of the IEC 60601-1-2 standard for EMC of medical electrical equipment. AAMI/FDA International Conference on Medical Device Standards and Regulation, McLean, VA, June 28-29, 2001.

Silberberg JL. Managing electromagnetic compatibility in the hospital. ACCE teleconference, July 19, 2001.

Silberberg JL. Achieving medical device EMC: The role of regulations, standards, guidelines and publications. 2001 IEEE EMC International Symposium, Montreal, Quebec, Canada, August 13-17, 2001.

Stern SH, Tucker SA, Gagne RM, Shope, Jr., TB. Estimation of benefit of proposed amendments to the FDA radiation-safety standard for x-ray equipment performance. FDA Science Forum, Washington, DC, February 2001.

Stewart SFC. Hydrodynamic testing of prosthetic heart valves: an FDA perspective. Fluid Mechanics Seminar Series, University of Maryland, College Park, MD, April 2001.

Stratmeyer ME. Ultrasound-induced experimental fetal bioeffects. 17th International Congress on Acoustics, Rome, Italy, September 2-7, 2001.

Wagner RF, Beiden SV, Campbell G, Metz CE, Jiang Y, Chan H-P. Multiple-reader studies, digital mammography, computer-aided diagnosis-and the Holy Grail of imaging physics. SPIE Conference "Medical Imaging 2001," San Diego, CA, February 17-23, 2001.

Wagner RF, Beiden SV, Campbell G, Metz CE, Jiang Y, Chan H-P. Multiple-reader studies, digital mammography, computer-aided diagnosis-and the Holy Grail of imaging physics. Workshop of the European Commission on Requirements for Digital Imaging, Malmo, Sweden, June 5-12, 2001.

Wagner RF, Beiden SV, Campbell G, Metz CE, Jiang Y, Chan H-P. Multiple-reader studies, digital mammography, computer-aided diagnosis-and the Holy Grail of imaging physics. Invited Tutorial, annual meeting of the American Association of Physicists in Medicine, Salt Lake City, Utah, July 23-26, 2001.

Wagner RF, Beiden SV, Campbell G, Metz CE, Jiang C.E., Chan H-P. Some observations on the assessment of emerging imaging technologies and the problem of the moving target. Medical Image Perception Conference IX, Warrenton, VA, September 20-23, 2001.

Waynant RW, Ilev IK , Mitra K. Waveguide delivery of x-rays for minimally invasive tumor therapy. Photonics West–BiOS 2001 International Conference, San Jose, CA, January 20-26, 2001.

Waynant RW, Ilev IK, Byrnes KR, Anders JJ. Low power laser irradiation increases axonal regrowth and cell invasion following acute spinal cord transection. FDA Science Forum, Washington, DC, February 15-16, 2001.

Wear KA. Anisotropy of attenuation and backscatter in human calcaneus. Journal of Ultrasound in Medicine, **20:**S1-S154, p. S:91, March 2001, 45th Annual Conference of the American Institute of Ultrasound in Medicine, Orlando, FL, March 11-14, 2001.

Wear KA. A model for ultrasonic backscatter from human calcaneus. Journal of Ultrasound in Medicine, **20:**S1-S154, p. S:91, March 2001, 45th Annual Conference of the American. Institute of Ultrasound In Medicine, Orlando, FL, March 11-14, 2001.

Wear KA. Relative roles of absorption and scattering in determining ultrasonic attenuation in calcaneus. International Symposium on Ultrasonic Imaging and Tissue Characterization, Arlington, VA, May 30-June 1, 2001.

Weininger S. Assuring the safety of pulse oximeters. AAMI Annual Meeting, Baltimore, MD, June 9, 2001.

Witters DM. Partnering for solutions: creation of new wireless medical telemetry service. FDA 2001 Science Forum, Washington, DC, February 16, 2001.

Witters DM. Update on medical telemetry's new dedicated frequency spectrum: FDA's concerns and recommendations. Capital Healthcare Engineering Society (NCHES), NCHES 5TH Annual Conference, First of the 21 Century, Andrews AFB, MD, May 8, 2001.

Witters DM. FDA concerns and recommendations for wireless medical telemetry. AAMI Conference Session: & Expo: Update on Changes in the Telemetry Spectrum, AAMI Conference and Expo 2001, Baltimore, MD, June 11, 2001.

Zmudzka BZ, Lao NT, Miller SA, van der Leun JC, Beer JZ. UV-induced erythema vs. skin type and race/ethnicity: visual and instrumental explorations. FDA Science Forum, Washington, DC, February 15-16, 2001.

Zmudzka BZ, Stamatas GN, Miller SA, Kollias N, Beer JZ. main components of UV-induced tan: pigmentation and erythema. 28th Annual Meeting of the American Society for Photobiology, Chicago, IL July 7-12, 2001.

Zmudzka BZ, Tadokoro T, Kobayashi N, Ito S, Wakamatsu K, Hearing VJ, Beer JZ. DNA damage induced by ultraviolet radiation vs. melanin content and production in human skin within racial/ethnic groups. 28th Annual Meeting of the American Society for Photobiology, Chicago, IL, July 7-12, 2001.

APPENDIX C – OST Academic Affiliations

October 1, 2000 – September 30, 2001

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 Adjunct Professor George Washington University Department of Electrical and Computer Engineering Adjunct Professor Catholic University of America Biomedical Engineering Department 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 Associate 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
Marlowe, Donald E.	Staff College Center for Devices and Radiological Health Food and Drug Administration Instructor/lecturer

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
Picciolo, Grace L., Ph.D.	Clemson University Department of Bioengineering Adjunct Professor
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 – OST Patents

October 1, 2000 – September 30, 2001

Mitra K, Waynant RW, Lambert. Method and apparatus for delivery of x-ray irradiation. US Provisional Patent Application Docket No.FIT 100P, Serial No 60/262,922. Filed January 19, 2001.

APPENDIX E – OST-Sponsored Seminars

October 1, 2000 – September 30, 2001

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

Gertsman BS. Laser radiation damage to biological tissue. Florida International University, May 16, 2001.

Hellman KB. MATES Initiatives – Overview and update, tissue reference group. Grand Rounds, Center for Devices and Radiological Health, Gaithersburg, MD, December 2000.

Hellman KB. Biotechnology/tissue engineering: forecasting, monitoring and assessment. Transmissible Spongiform Encephalopathies (TSEs) and Product Safety, Center for Devices and Radiological Health, Gaithersburg, MD, August 23, 2001.

Hewlett IK. CBER, FDA, Bethesda, MD. Studies on HIV Pathogenesis and Diagnosis. Center for Devices and Radiological Health, Rockville, MD, October 24, 2000.

Ilev IK. Modern photonic delivery, sensor, and imaging techniques in biomedicine. FORCE Seminar to the FDA/CDRH Staff College, Rockville, MD, May 22, 2001.

Pfefer TJ. Minimally invasive optical diagnostics. CDRH Grand Rounds Science Seminar, U.S. Food and Drug Administration, Rockville, MD, February 6, 2001.

Risby T. Use of breath analysis to look at tissue injury and disease. Johns Hopkins School of Public Health, Baltimore, MD, April 17, 2001.

Squier J. Viewing the microscopic world through the application of ultrafast technology. University of California at San Diego, San Diego, CA, August 31, 2001.

APPENDIX F - Research Contracts, Interagency Agreements and Cooperative Research and Development Agreements

October 1, 2000 – September 20, 2001

Air Force Office of Scientific Research (AFOSR) (FDA-224-98-6005). Infrared fiber and wavelength testing for the Air Force.

Air Force Office of Scientific Research (AFOSR) (FDA-224-01-6003). Waveguide and fiber optic delivery for medical applications of FELs.

Armed Forced Institute of Pathology (AFIP) (FDA-224-82-5000). Tissue preparation and analysis of cardiovascular tissue specimens.

Biocon, Incorporated (FDA-223-99-6052). Housing, care and welfare of experimental animals.

Cellular Telecommunications Industry Association (CTIA) (CRADA). Health effects of RF emissions from wireless phones.

Department of Defense/Uniformed Services University of the Health Sciences (DOD/USUHS) (FDA-224-98-6015). Maintenance of an animal of the pathophysiology of diabetes for end organ studies.

Department of Energy/Oak Ridge Institute for Science and Education (DOE/ORISE) (FDA-224-88-6064). Establishment and conduct of a research fellowship program.

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

Federal Aviation Administration (FAA) (FDA-224-00-6061). Medical device electromagnetic interference research and testing with medical devices.

National Aeronautics and Space Administration (NASA) (FDA-224-98-6013). Evaluation and testing of a novel fiber optic eye diagnostic instrument in an animal model of diabetes.

National Aeronautics and Space Administration (NASA) (FDA-224-01-6001). Promoted ignition testing of medical oxygen regulators.

National Research Council (NRC) (FDA-223-99-6051). National Research Council Associateship Program for the Food and Drug Administration.

APPENDIX G - Abbreviations and Acronmyms

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
FDLI - Food and Drug Law Institute
FDA - U.S. Food and Drug Administration, PHS, DHHS
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
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

DDL	- Devices and Diagnostics Letter (also known as The Orange Sheet) (Weekly Trade Magazine)
DCRND	- Division of Cardiovascular, Respiratory and Neurological Devices, ODE
DCLD	- Divison of Clinical Laboratory Devices, ODE
DECS	- Division of Electronics and Computer Science, OST
DGRD	- Division of General and Restorative Devices, ODE
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
DPS	- Division of Physical Sciences, OST
DRAERD	- Division of Reproductive, Abdominal, ENT, & Radiological Devices, ODE EIR - Establishment Inspection Report
EMC	- Electromagnetic Capability
EMI	- Electromagnetic Interference
ERC	- NSF Engineering Research Center, Duke University (National Science Foundation)
510(k)	- Five-Ten K: Premarket 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)
OCD	- Office of the Center Director, CDRH, FDA, DHHS
OC	- Office of Compliance, CDRH, FDA

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