OFFICE OF SCIENCE AND TECHNOLOGY

Annual Report

Fiscal Year 2000

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 purpose of the OST Annual Report is to update our readers about OST's organization, staffing, and intramural science activities; provide a summary of our direct lab support for premarket review and compliance cases; and provide a bibliography of scientific publications, presentations, contracts, patents, and research seminars of the Office for fiscal year 2000. The Annual Report is an overview rather than a comprehensive accounting. For additional information, please contact us. The report might also be viewed as a source of information regarding areas in which Cooperative Research and Development Agreements (CRADAs) can be initiated with interested institutions. OST welcomes comments on the programs described in this report. We hope you find this report useful and informative, and we invite any comments you might want to offer.

Donald E. Marlowe
Director
Office of Science and Technology

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October 1, 1999 – September 30, 2000

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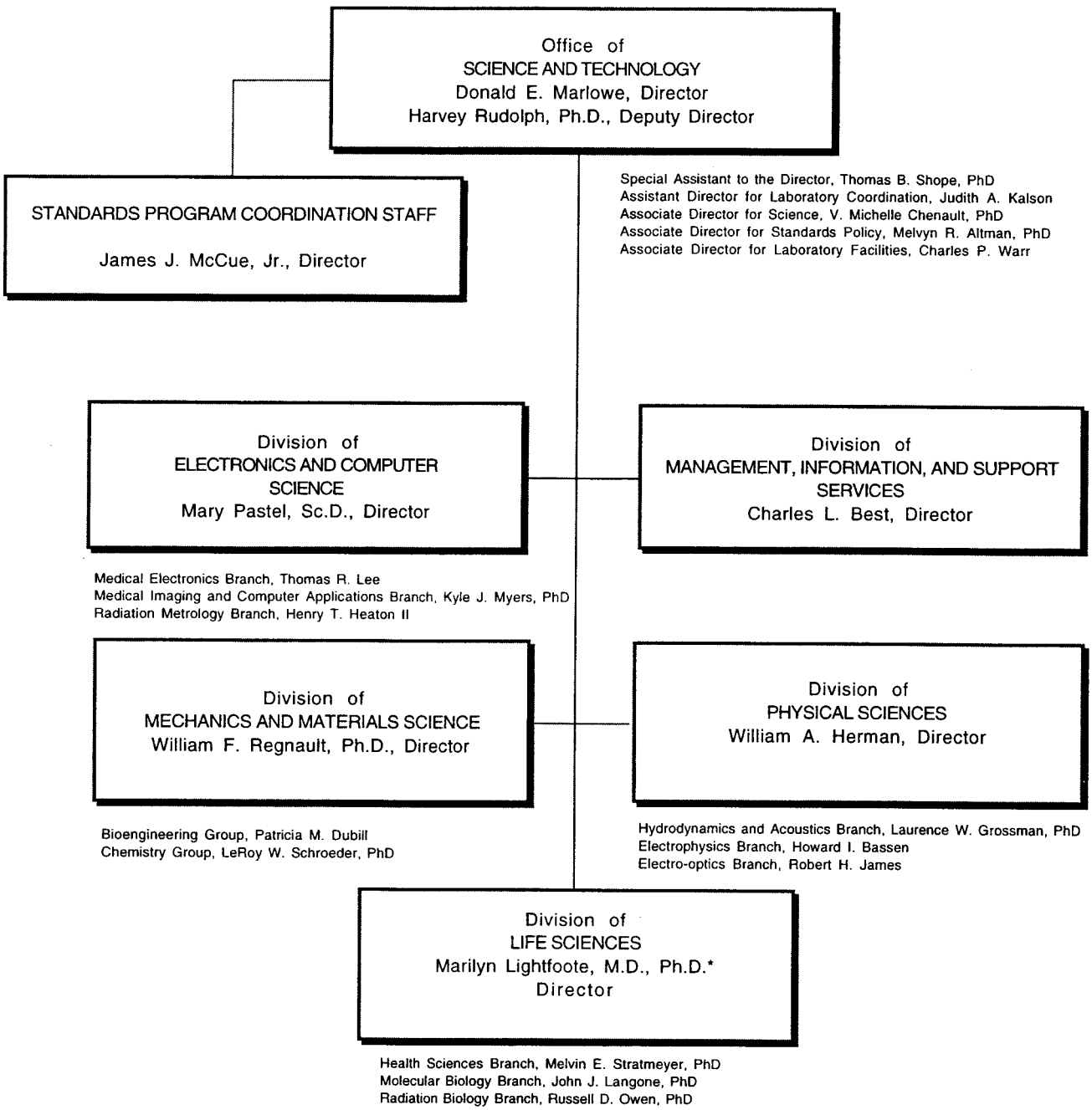
OFFICE OF SCIENCE AND TECHNOLOGY
Organization Chart



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OFFICE OF SCIENCE AND TECHNOLOGY PROGRAMS

ARTIFICIAL ORGAN REPLACEMENTS AND ASSISTS

Advances in the development of artificial organs 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 this technology interacts with the body so as to identify key questions early for CDRH. Projects also include development of meaningful test methods. In FY 2001, OST investigated a number of issues related to the successful use of artificial organs and organ assists including 1) cavitation damage to prosthetic heart valves, 2) damage to blood components following implant surgery, 3) test methods for implantable infusion pumps, 4) blood flow thru implants, 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 of manufacturers' submissions. The on-going work in the areas of heart valves, blood damage, and hemodialysis is directly coupled into regulatory guidance and standards-setting activities. For example, there are on-going validation round-robin experiments involving both manufacturers and FDA in the area of heart valves. These experiments have grown out of the experimental work conducted in the area by OST over a number of years. This program also provided input to the development of ANSI and ISO standards on refractive implants and multifocal IOLs. Laboratory work on electrical stimulation was used to help formulate a guidance document for spinal cord stimulators, and in the revision process for national standards for nerve stimulators. Additionally, this research served as a basis for the premarket review of a number of investigational sense-organ replacement devices.

A New Flow Visualization System for Quantifying Flow in Artificial Organs
Key words: flow visualization, DPIV validation model, and standard test method

A new Digital Particle Image Velocimetry (DPIV) flow visualization system was developed this year incorporating a state-of-the-art dual pulsed YAG laser and fiber optic link. This new tool quantifies flow patterns from artificial organs such as heart valves, vascular grafts, artificial hearts, blood pumps, etc. It can identify aberrant flow patterns which may cause blood damage and device failure. When blood flow is too slow, dangerous blood clots can form; when blood flow gradients are too high, red blood cells are destroyed.

A block diagram of this system is shown in the figure below. The system uses two laser flashes to freeze the motion of particles seeded in the moving fluid. A high-speed digital camera captures the images produced by the laser pulses. A computer calculates fluid velocity by correlating particle positions in the two images.

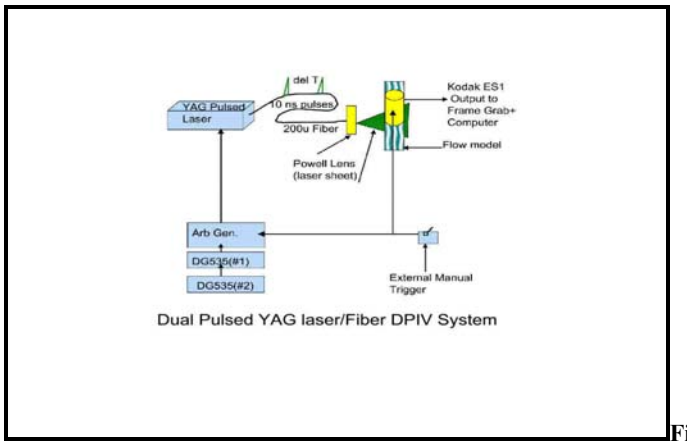

Figure 1. This system was validated and used to measure flow through a St. Jude mechanical heart valve. The figure below shows a sample measurement obtained with the DPIV system that demonstrates the tri-jet flow pattern for this triple orifice valve.

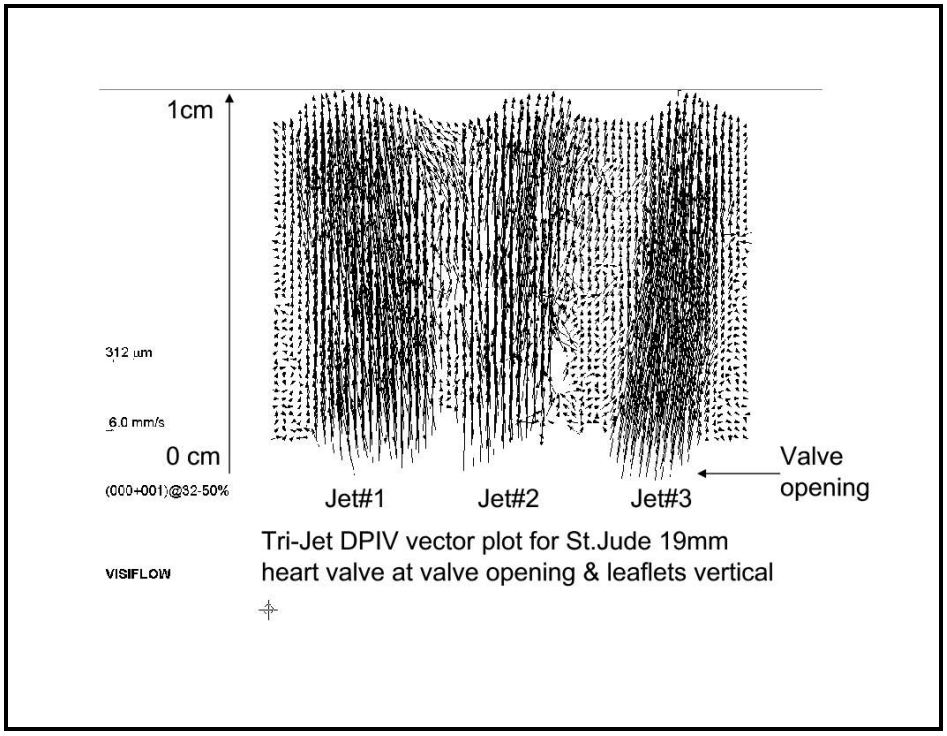

Figure 2

Ophthalmic Implants

Key words: intraocular lenses, refractive implants, standards, technical support

OST continues to participate in the Center's enforcement program for intraocular lens implants (IOL's) by developing and using test methods to assess IOL optical properties, such as refractive power and resolution. During FY 2000, several samples of IOLs were tested in the OST laboratory. Staff scientists are also participating in voluntary standards activities for IOLs on the ANSI Z80 subcommittees for optical engineering issues. The present ANSI Z80.7 standard for Intraocular Lenses is in the process of being harmonized with the ISO 11979 series. Additionally, there are two new IOL standards being developed in ANSI Z80 - Z80.12 (Multifocal Intraocular Lenses), and Z80.13 (Refractive Implants). These standards have also been accepted by the International Standards organization (ISO) for consideration as international standards. In the first half of FY 2001, OST will participate in a ring-test on Modulation Transfer Function (MTF) calculations (computer modeling) for a number of multifocal IOL designs.

Safety of High-Rate Nerve Stimulation

Key words: neuron, computer simulation, cochlear implant, spinal cord stimulator, brain

This project assesses the safety of rapid-rate nerve electrical stimulation at rates higher than nerve impulses can follow. This simulates the energy delivered by new-generation neurological implants. OST scientists examined the physiological effects of such stimulation in real and computer-simulated nerve cells. As pulse-rate is increased, nerve firing followed the stimulation. Then, as the rate increased further, the firing decreased, increased and finally (at highest pulse-rates) the nerve stopped firing and became refractory to stimulation. Even when pulses are subthreshold, rapid-rate pulses alter neural excitability. This work, for the first time, gives quantitative measures of nerve stimulation efficiency. It forms the basis of questions in regulatory reviews and improves the design of rapid-rate stimulation.

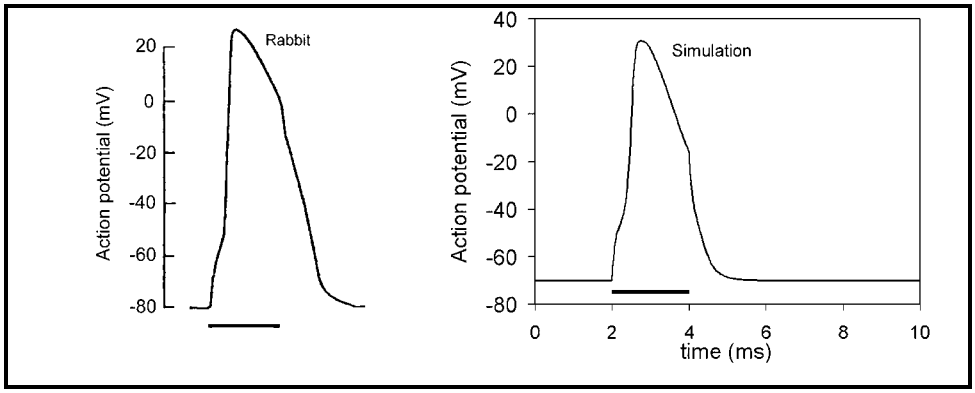

Figure 3: Action potential in real rabbit myelinated axon (left trace) as compared to computer-simulated rabbit axon (right trace, the solid bar in each trace represents a 2 millisecond, 0.2 nanoampere stimulation pulse).

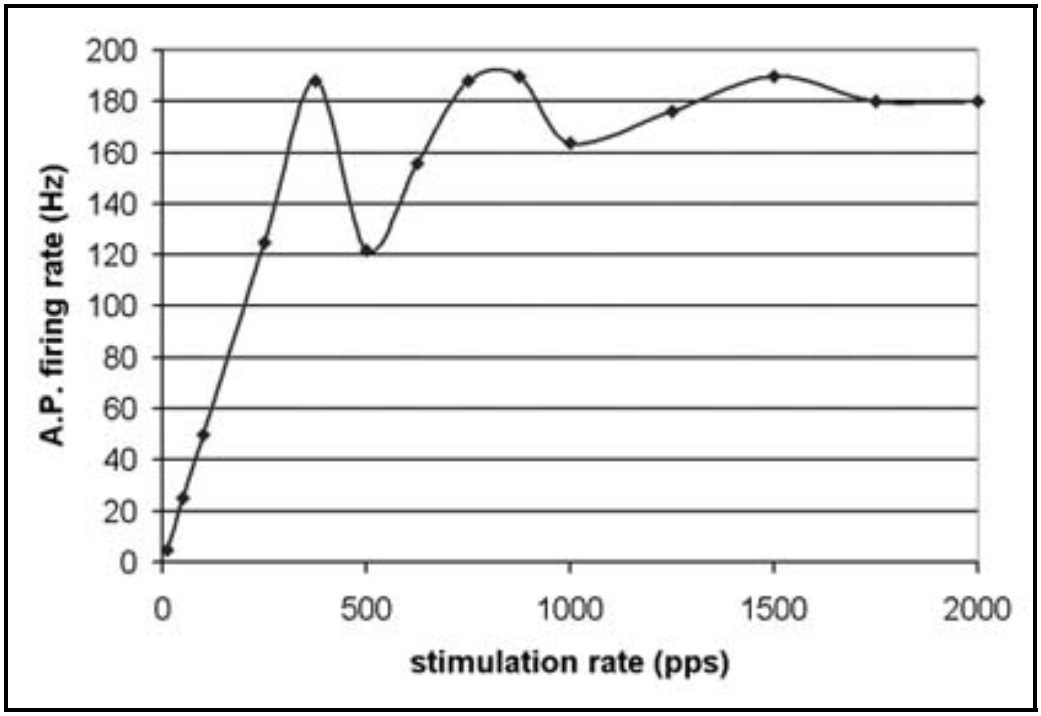

Figure 4: Relationships between stimulation rate and action potential (A.P.) firing rate.

Examination of Mechanical Prosthetic Heart Valve Closing Sounds for High Frequency Acoustic Energy as a Signature of Cavitation

Key words: cavitation, acoustic, heart valves

Transient cavitation has been observed near operating mechanical heart valves. This cavitation, the formation and very rapid collapse of tiny bubbles, can cause valve damage or influence the hemolysis associated with these valves. FDA requires the manufacturers of mechanical heart valves under review to test for the presence of induced cavitation. OST is currently examining the available tests for cavitation. Previous studies to develop an acoustic technique detecting cavitation in and around mechanical prosthetic heart valves encountered a new problem. Not only does the collapse of cavitation bubbles causes high frequency noise; the mechanical action of valve closing, as well as the pump used to actuate the valves, also causes a broad band high frequency signal. In an attempt to distinguish cavitation noise from irrelevant sources, more data from different types of mechanical valves were taken. Spectra from time windows offset with varying time delays from valve closing were also captured to try to separate valve noise from cavitation noise. These data are currently being analyzed. Also, a new system using a sensor resonant at very high frequency (2 MHz) was put in place, and data will be taken at a higher frequency range for the universe of valves being studied.

Simplified Bernoulli Relation and Artificial Heart Valves
Key words: Bernoulli, heart valves, pressure drop.

Clinicians utilize Doppler ultrasound devices to determine the blood velocity near heart valves. A theoretical relationship, the Simplified Bernoulli equation ($P = 4V^2$), is then commonly used to calculate the transvalvular pressure gradient, an important indicator of valve performance. A study has begun in OST to determine how well this relation applies to currently marketed prosthetic heart valves, since prior studies have shown that the Bernoulli constant of 4 is not always appropriate. *In vitro* test data reported to the FDA by valve manufacturers shows a range of 1.5-8.0 for the constant. With data taken for the entire range of valves available for implantation, the current study is designed to resolve whether the variation is a real effect or primarily due to measurement error. The study comes as the ISO 5840 international heart valve standard and FDA heart valve guidance are under revision.

Blood Flow and Pressure Transducer Protectors in Hemodialysis Machines
Key words: hemodialysis, transducer protector, pressure

In May 1999, FDA issued a Safety Alert in conjunction with a manufacturer's recall of hemodialysis blood tubing sets due to blood contamination within the tubing's pressure line transducer protectors. Due to the large number of people undergoing hemodialysis in this country (approximately 250,000), OST began a study as to how blood contacts the pressure line transducer protectors in hemodialysis machines. Blood contact may prevent accurate pressure monitoring and lead to contamination of the machine's internal tubing. The blood level may rise in the bubble traps due to air leaks in the pressure lines, air entrainment in the flowing blood, air-blood mixing causing foaming, and air compression due to increased flow resistance. Air leaks are especially serious since they can allow blood to contact the transducer protectors without activating the pressure alarms.

Neurological CSF Shunts
Key words: neurological shunts, CSF shunts, hydrocephalus, *in vitro* performance testing

Testing has been underway to address problems associated with neurological shunts used to treat hydrocephalus. Currently, there exists an ASTM standard for these devices. However, this standard has been criticized as not being predictive of *in vivo* performance. Preliminary test results from this shunt evaluation have shown variable performance that does not match data provided by the manufacturer. In order to further understanding of CSF shunt performance, several shunt models from different manufacturers have been acquired in larger numbers and will be evaluated using the ASTM standard. This will allow a better statistical determination of shunt performance *in vitro* and will enhance understanding of the suitability of the ASTM standard to currently marketed shunt designs. This may ultimately lead to the development of more appropriate test methodologies for CSF shunts.

Large Animal Models of Vascular Disease and Therapeutic Device Interventions
Key words: minimally invasive techniques, vascular disease, angioplasty, radiofrequency ablation, re-clinical animal models

CDRH has established a large animal cardiovascular research program to develop and study models of cardiovascular disease and therapeutic device interventions. OST scientists are studying the effects of gender and hormone state on 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. OST is also examining the biophysics of radiofrequency ablation for the treatment of hepatic 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.

BIOMATERIAL EFFECTS ON IMMUNE SYSTEM

A biomaterial in a medical device in contact with mucous membranes or blood may leach into tissue and initiate a local response such as inflammation. This normal inflammatory process can become pathologic under chronic conditions and result in unresolved granuloma formation. Chronic perturbation of the immune system characterized by episodes of inflammatory bursts can break biological tolerance. Immunological defense mechanisms such as those involving cellular elements of the inflammatory process, the complement cascade, and cell proliferation can (under chronic conditions) damage tissues. This occurs when the normal inflammatory process becomes pathologic and results in granuloma formation and arthritic-like symptoms.

From a regulatory perspective, immunotoxicity is defined as any effect on the structure or function of the immune system or on other systems as a result of immune system dysfunction. An effect is considered adverse or immunotoxic if it impairs humoral or cellular immunity needed by the host to defend itself against infections or neoplastic disease or causes unnecessary tissue damage. It is essential to clearly recognize that change in an immune function or level of immunological mediator may not necessarily appear as an adverse effect, but rather as immunostimulation. Decisions on whether a material/device is immunotoxic must rely on the available evidence from preclinical test results and clinical evaluation, as well as prior history of use. Because the available data will often be less than conclusive, good judgment will play an important part in evaluating immunotoxic risk.

A goal of the OST research program is to provide laboratory assessment of the types of testing available for evaluating potential adverse effect of biomaterials on the immune system and to provide a process for selecting appropriate test

methods. OST aims to make it possible for reviewers to obtain adequate information to make confident regulatory decisions; to ask the appropriate questions when negotiating with manufacturers; and to generate independent data concerning immune responses to biomaterials in devices. The data should provide some level of assurance that immunotoxic reactions are unlikely.

OST scientists have served as members of ODE review teams for McGhan Gel-filled breast Implants, for Mentor Silicone Breast Implants; for gene kit components, PDP devices and humanitarian devices exemption submissions (including a request for a toxicological consult regarding the carcinogenicity of gluteraldehyde). Scientists contributed reviews of master files and guidance documents.

Staff developed and coordinated IMMUNOTOX, an online service available on FDA intranet/FIRST to enhance communication among FDA immunologists and immunotoxicologists and to provide online services. The goal of the service is to provide assistance on product-related regulatory review issues.

The regulatory impact of immunotoxicity was addressed in the **Immunotoxicity Guidance for Reviewers and Industry**, prepared by staff scientists. The guidance was derived, in part, from laboratory studies and literature review and is designed to provide assurance that immunotoxic reactions are unlikely.

Finalization of a Standard Practice for Testing for Alternative Pathway Complement Activation in Serum by Solid Materials

Key words: complement activation, alternative complement pathway, medical materials, standard

This Standard Practice was developed by OST scientists and has been accepted by ASTM as "Standard Practice for Testing for Alternative Pathway Complement Activation in Serum by Solid Materials." Complement activation by the alternative pathway is a potential hazard when a patient's blood contacts medical device materials. Inappropriate complement activation by blood-contacting medical devices may have serious acute or chronic health effects. This practice provides a protocol for simple, inexpensive, rapid, *in vitro* screening for alternative pathway complement activating properties of solid materials used in the fabrication of medical devices that will contact blood. The practice is designed for use with other standards that assess the biocompatibility of materials, particularly a previous standard also developed by OST scientists: ASTM F1984-99 "Standard Practice for Testing for Whole Complement Activation in Serum by Solid Materials." The practice is composed of two parts. In the first part, serum from guinea pigs genetically deficient in the complement factor C4 (necessary for classical pathway complement activation) is exposed to a solid material, during which alternative pathway complement activation and depletion of key complement proteins may occur. In the second part, the remaining complement is assayed for its ability to lyse rabbit red blood cells via the alternative pathway. The unsuitability of using human serum depleted of C4

by column immunoabsorption is discussed. Data demonstrating the equivalence of guinea pig serum to human serum for detection of complement activation by biomaterials, such as beaded agarose (Sepharose), is presented. Whereas some assays identify the amount of individual complement proteins in the blood, this assay determines alternative pathway complement functional activity. Therefore, the standard practice examines the ability of complement to exert one of its primary functions: the lysis of target cells. Assessing *in vitro* alternative complement activation, as described here, provides one method for predicting potential complement activation by materials intended for clinical application in humans when the material contacts the blood. This *in vitro* test method is suitable for adoption in the specifications and standards used for screening solid materials used in constructing implantable medical devices or devices that come in contact with human blood outside of the body.

Complement Activation by Implanted or External Blood-Contacting Medical Devices

Key words: alternative pathway, complement activation, standards.

Complement is a series of serum proteins involved in mediating immune reactions. Complement activation is a tightly regulated process that, in addition to direct cell cytolysis, can have profound affects on the immune, vascular, and coagulation systems. Though complement activation is an important defense mechanism against microbial infections, inappropriate activation by implanted or external medical devices may result in serious acute or chronic reactions.

Complement activation can occur by two main pathways. The *classical pathway* is triggered by antibodies bound to a cell surface. The *alternative pathway* is triggered by free hydroxyl or amino groups, such as are present on microbial organisms. Medical device materials generally activate complement by the alternative pathway. Complement activation by a candidate material via the alternative pathway *in vitro* indicates the material's potential to trigger inappropriate complement activation when implanted in a patient or placed in contact with the patient's blood outside the body.

OST scientists finalized a Standard Practice, accepted by ASTM, which screens specifically for alternative pathway complement activation by solid materials used in manufacturing medical devices. This supplements ASTM Standard Practice F1984-99, also developed by OST scientists, which screens for complement activation but does not specify which pathway is activated.

Examples of devices whose materials might activate complement by the alternative pathway include perfusion devices (such as dialysis membranes, cardiopulmonary assist systems, biosensor membranes, liver-assist perfusion devices, and columns for removing antibodies and other factors from patient blood), indwelling artificial vascular grafts, encapsulated drugs or cells, and vascular shunts/stents/catheters. OST is conducting research to acquire baseline information related to assessing risk from complement activation, particularly via the alternative pathway, by these devices.

In particular, complement activation by cardiovascular devices is being studied in a pig model. OST scientists are developing standardized methods to study complement activation by cardiovascular shunts, catheters, guide wires, and stents. The serum taken from pigs has been assayed before and after balloon angioplasty, and the scientists have documented a small but significant decrease in systemic whole complement levels, suggesting that complement activation does indeed occur during the procedure. The possible association of device-mediated complement activation in reblockage (restenosis) of unblocked cardiac arteries is also a concern.

Since damage by cardiovascular devices to the endothelial cells lining the inside of the blood vessels is known to be a critical step in subsequent restenosis, methods were developed for determining the effect of complement on pig and human endothelial cells via flow cytometry and fluorescent dyes. OST data demonstrated that complement activation by the classical and alternative methods both produce significant lysis of endothelial cells. OST researchers are now developing methodologies to extend the data to intact monolayers of pig and human endothelial cells, as a model of the interior of device-disturbed blood vessels.

Analysis of Autoantibody Responses to Silicone Gel-Filled Breast Implants
Key words: autoimmune disease, autoantibodies, silicone breast implants, silicone gel

Autoimmune diseases have been reported in women with silicone breast implants. The presence of autoantibodies in some of the women, as well as studies in experimental animals, suggest that silicone may play a role in these adverse effects on the immune system. Earlier OST studies have shown that silicone gel/oil can promote autoantibody production against the connective tissue proteins, collagen, and can migrate from the implant site to other parts of the body. The current project is a confirmation study. There were 240 rats from 2 different strains used in this study: Dark Agouti and Sprague Dawley. Rats were divided into six groups: immunized with Dow Corning oil, silicone oil with/without rat collagen type I/II, Dow Corning gel, silicone gel with/without collagen type I/II, incomplete adjuvant with collagen type I/II, and rat collagen I/II. Rats were pre-bled before the immunization and every 4 weeks after the initial immunization. Sera were tested for antibodies against rat collagen type I, and rat collagen type II using ELISA technique.

COMPUTATIONAL MODELING

Continuing advances in computer power are now making computational modeling a powerful tool for evaluating new devices. Product designers are making increasing use of such modeling in the development and evaluation of new technologies and products. These techniques allow both designers and FDA scientists to manipulate a wide range of variables without having to construct a laboratory bench test mechanism for each possibility. Moreover, a well-optimized

complementation of clinical trials with computer modeling holds excellent promise for both reducing costs and increasing the informational value of such trials. In FY 2000, OST investigated these modeling techniques with the goal of assisting manufacturers in the analysis their products through the use of computation methods where cost/benefit advantages exist. Sponsors are increasingly turning to computational modeling to provide answers to problems not answerable by other techniques, and this is particularly true for heart valve technology. In FY00, OST scientists reviewed a number of applications where computational modeling provided the best available estimate of the large transient stresses induced in mechanical heart valves when the valve slams shut. This program also contributed to the development of the ASTM Standard Test Method for Measurement of Radio Frequency Induced Heating near Passive Implants in the Magnetic Resonance Imaging (MRI) Environment and to the review of device applications with claims of MRI compatibility and safety.

MR Compatibility: Evaluation of Patient Heating

Key words: magnetic resonance imaging radiofrequency MRI safety, Implants, SAR, magnetic fields

This project is investigating the use of computer modeling to evaluate the undesirable heating of certain patients undergoing magnetic resonance imaging (MRI) examinations. This heating occurs because of the interaction of metallic implants with the strong radio frequency (RF) magnetic field produced by a MRI device. Commercially available software XFDTD was adapted to model and calculate the rate of RF energy absorption (Specific Absorption Rate or SAR) and the SAR distribution in a realistic model of the human body. The body model contains a metallic implant and is placed in a model of birdcage body coil of a 1.5 Tesla MRI (RF magnetic fields at 64 MHz). The result of extensive computations show that the magnitude of the increased tissue heating due to the presence of the metallic implant depends on the dimensions, the orientation, the shape of the metallic objects, and the location of the metallic implants in the patient. The increased heating of surrounding tissues primarily concentrates in a small volume near the tip of the metallic wire. Scientists obtained a calculated maximum SAR value of 41 W/kg (averaged over one gram of tissue) at this location. However, a maximum value of 310 W/kg was calculated when the absorption is averaged over 0.125 gram of tissue.

Calculation of Virus Transport through Barriers as a Function of Pore Geometry

Key words: virus transmission, transport modeling, computational fluid dynamics, barrier evaluation

When stressed during use, synthetic barriers such as surgical gloves can develop tears that are undetectable by the user. While post-operation tests can detect the presence of holes in the glove, they provide little information regarding how much virus may have been transmitted during use. OST scientists employed a mathematical model to predict levels of virus transmission through a compromised barrier as a function of pore

geometry and trans-membrane pressure. It was found that during conditions modeling the manipulation of surgical instruments, up to 300 hepatitis B viruses per second are transmitted through a slit 1 micron high and 4 microns wide. The calculations help CDRH to meaningfully quantify the risk associated with barrier failure.

Computational Studies of Vascular Grafts
Key words: vascular grafts, blood flow, modeling methods

A computational study has begun to determine how vascular prostheses affect blood flow and the concentration of chemicals activated by the prosthetic material. Earlier studies have shown trapped particles at the downstream junction between a graft and artery, which correlates well with the clinical finding of increased tissue overgrowth there. Preliminary computational studies also show an enhanced concentration of dissolved species at this site. This study aims to elucidate factors leading to clinical graft failure and to provide expertise in modeling methods likely to be used in future applications of endovascular grafts, stents, and other cardiovascular devices.

DEVICE PERFORMANCE ANALYSIS AND MODELING

The development of test methodologies and performance requirements for devices and materials are vital for industry's consensus standards. OST's program has two areas of focus. The first is developing chemical test methods that determine the accuracy and precision of analytical instruments or the performance of devices that rely on mass transfer. The second is developing test methods for devices and materials involving performance requirements such as strength, durability, abrasion resistance, puncture resistance, etc. This program area allowed OST to participate in the technical reviews of numerous new products such as bioprosthetic heart valves and tissue adhesives.

Endovascular Stent Standards Development
Key words: stents, standards, test methods

OST laboratory personnel, in collaboration with ODE and industry and under the auspices of ASTM, are continuing to develop detailed test procedures for clinically relevant engineering attributes of endovascular stents. The ASTM Interventional Cardiology Task Group, co-chaired by OST and supported by data generated by the OST laboratory effort, has completed work on two standards. The data to support precision and bias statements for these methods are being developed. Significant effort was spent evaluating the details of stent dimensional characterization, including the diameter measurements used for the calculation of recoil. The stents on hand were characterized by a variety of methods (profile projection, pin gages, laser micrometer, calipers) with a view toward quantifying both the precision of the method and the variation in dimension

across the stent. Preliminary data indicate that further development of the methodology is necessary if the precision goals for the standard test methods are to be met.

EMERGING ISSUES 2000: GENETIC TECHNOLOGIES

The revolution in human genetics and the sequencing of the human genome will create new opportunities for public health and new challenges for FDA. CDRH is preparing for the capability of assessing and regulating genetic testing devices within the near future. OST organized meetings with ODE senior staff to assess the role of genetic testing in CDRH. Staff presented grand rounds and updates on emerging science issues. The FDA Science Forum was organized. OST scientists served as members of scientific advisory committees for other FDA Centers, and taught courses on biocompatibility to update review staff. Information sessions, including presentations by developers of genetic and genomic technologies, have been organized by ODE's Division of Clinical Laboratory Devices. Scientists in OST's Division of Life Sciences have aided the recruitment of speakers and contributed actively to the discussions. OST is also involved in the FDA Genomics/Proteomics working group, organized by the Commissioner's Office. This group is developing priorities for action related to FDA readiness in assessing new genetic technologies.

OST scientists are developing laboratory projects to develop hands-on readiness for the emerging technologies. These projects will provide a base for keeping up with the technologies as they evolve. It is also expected that they will demonstrate some of the ways in which new genetic approaches can enhance human health. There are two quite different types of devices representing the new technology expected to come to CDRH for review: ***genomic*** or ***genetic*** testing devices.

Laboratory projects in genetics testing and genomics are developed to enhance the reviewer readiness for emerging technologies involving the genome revolution. Models derived from these studies are useful to derive standards related to identification of genotoxic components of medical devices (including dyes in sutures, surgical sealants, etc.) and assessment of genetic testing components.

The ***genomic type*** involves gene expression, often in comparison to a reference population. This involves analyzing many hundreds or thousands of genes that are up-regulated or down-regulated in response to a stimulus. The result is a pattern of gene expression that is designed to be diagnostic or characteristic of a particular subset of the population. For this type of device, data organization and assessment, i.e., bioinformatics, are important. Examples would be a pattern of gene expression related to toxic responses and other adverse events.

The second type of assessment is a ***genetic test*** to determine the presence or absence of a particular DNA sequence already known to be related to a health outcome. In practice, this is a yes or no question, independent of signal size. Examples are mutations in the cystic fibrosis gene (human genetic disease), in a drug metabolizing gene (adverse event from a particular class of drug), in the p53 gene of a tumor (diagnostic for cancer), or in genes related to susceptibility to cardiovascular disease. Pharmaceutical companies are planning to submit genetic testing devices along with drugs in order to stratify a clinical trial population, or to include or exclude a certain segment of the population, resulting in a customized therapy. The goal is to identify a smaller and more appropriate clinical trial population.

The technological issues in insuring the safety and efficacy of these two different types of genetic testing devices are different. It is important to address both sets of issues.

OST has developed projects in each area that can be used as a basis for investigations into the issues affecting the safety and efficacy of *genetic* and *genomic* devices.

Genomic devices. A project to develop a gene expression pattern characteristic of latex sensitivity is being developed in collaboration with the CDRH Offices ODE and OSB, with CBER, and with a small biotech company. This project allows OST to gain data and experience. OST scientists expect to establish gene chip technology in the future. The gene expression model could be used to develop methods for evaluating new biomaterials, such as those resulting from tissue engineering. With an in-house system, OST could offer to partner with ODE in identifying technological sources of error in chip devices (e.g., reproducibility of oligonucleotide sequence and quantity deposited). These issues could then be addressed in standards and guidelines for approval of these devices. Collaboration between OST's Division of Life Sciences and Division of Electronics and Computer Science could be established in the area of data management, bioinformatics, and pattern recognition.

Genetic devices. Genetic testing and genetic susceptibility testing involve the resolution of single-base pair differences in DNA, usually by hybridization to specific oligonucleotides. OST has a project in this area utilizing the human p53 gene. The project involves assessing sequence changes in the p53 gene using both conventional and microarray technologies. This project serves as a model for genetic testing related to diagnosis, prognosis, and therapy of many types of cancer. It may also be used as a model for standards development related to identification of genotoxic components of medical devices. These include dyes in sutures and other products, components of surgical sealants, and some types of breast implants.

Development of an In Vitro P53 Human Gene Mutation Assay for Cancer Risk Studies

Key words: p53, cancer risk, mutation, genetic testing, genetic devices

There is a great need for more relevant tests for evaluating the cancer risk of medical devices and low frequency radiation. This includes assessing the genotoxic constituents of medical device materials, e.g., those in surgical sealants and bone cement (t-butylhydroperoxide and hydroquinone), as well as implants (toluenediamines). Dyes associated with medical devices can be genotoxic. Assessing the long-term risk of devices emitting low frequency radiation, including cellular phones, is also problematic. Recent findings in cancer research have shown that a substantial proportion of human tumors has mutations in the p53 tumor suppressor gene, 50% on average, but varying by tumor type. These mutations cause loss of genome integrity and cellular growth control; evidence is accumulating that these mutations are directly related to cancer development in humans. Among the most compelling data are the cases in which p53 signature mutations, characteristic of the environmental agents to which a population has been exposed, are found in their tumors.

In assessing human cancer risk, therefore, one important question is whether a biomaterial, breakdown product, impurity, or other relevant substance or device has the capability of causing mutations in critical regions of the p53 gene. There are no currently available practical means of determining this. Therefore, OST has worked to develop a standardized screening assay for measurement of mutation induction in the p53 gene. Until recently, it has not been technically feasible to easily identify and select p53 mutations. However, several laboratories have developed methods for identifying p53 mutations introduced into yeast. A recently constructed version of the yeast, created at MIT, carries a plasmid carrying p53 cDNA and two genes that are transactivated by wild-type p53 protein. The strain is engineered such that p53 mutants have a double mutant phenotype allowing mutant identification by color and mutant growth advantage on selective media. OST acquired this strain and have made progress in developing a p53 mutagenicity assay for routine screening purposes. By varying conditions of culture growth, temperature, media components, concentration (the chemical used in the p53 mutation assay), age of plates, and incubation time, scientists established conditions for optimum selection of yeast having p53 mutations. In a reconstruction experiment, OST scientists demonstrated the recovery of 10 mutants in a background of 10^5 or 10^6 non-mutants. Scientists determined that several variables are critical in reproducible selection of mutants (temperature, plate age). By selecting for linked markers, OST developed simple tests to monitor for loss of the two plasmids. Other experiments have studied the role of media, temperature, growth stage, and expression time on mutation generation and recovery. Initial experiments with UV radiation were successful in generating p53 mutants, although the doses have not been optimized. OST explored ways of accomplishing mutant expression and selection on one plate, to make the assay as functionally simple as the Ames Salmonella plate assay; but this has not yet been achieved. There has been good progress in developing a more relevant tool for assessing cancer risk.

FAILURE ANALYSIS OF ELECTRONICS IN MEDICAL DEVICES

OST applies readily available tools and methods to the laboratory evaluation of medical device performance. OST also applies analytical tools to problems of medical device reliability. These programs are directed at identifying generic device electrical engineering problems and their solutions. The principal laboratory activities are to design and develop specialized test equipment, evaluate failed medical devices, and develop test methods. Areas of particular laboratory interest include microcircuits, batteries, and electrical fires.

Regulatory Support - Forensics

Key words: electronics, forensics, regulatory support, fire

OST provided laboratory forensic support for several FDA regulatory actions. In one, an OST engineer played a significant role in a case involving the explosion of a lithium sulfur dioxide battery in a portable defibrillator. The battery in question used a newly emergent technology. This technology offers significant performance advantages over more established battery chemistries, but hazards associated with the new product were not well understood by the manufacturer. OST's investigation revealed that at least one other manufacturer of portable medical devices has grappled with these issues.

In another compliance case, one involving an infusion pump, it was determined that defective battery “gas gauge” software caused a rechargeable battery to be depleted to the point that physical damage occurred in one or more cells, resulting in premature failure of the battery. An OST engineer participated in an on-site inspection of the firm, which prompted a product recall.

OST engineers provided regulatory support in several other cases involving electrical safety. In one case, OST developed a test apparatus for assessing the compliance of medical device connectors with the *CDRH Standard for Electrode Test Leads and Patient Cables*. In another case, cable assemblies from a surgical device were tested for compliance to IEC 60601-1. In a third case, OST investigated a recall situation involving a neurological testing device that was manufactured by both a U.S. and Canadian firm under a license agreement. The U.S. firm determined that the design was not compliant with electrical safety provisions of IEC 60601-1 and instituted a recall on that basis. The Canadian firm disagreed with this assessment and declined to recall. OST determined that the product was indeed non-compliant. A fourth case involved a complaint brought by a competitor against a cardiac assist device, in which it was alleged that the device violated an electrical safety standard to which compliance was claimed. OST determined that the design did not violate the standard and the manufacturer was exonerated. In a fifth case,

OST assisted in the field investigation of an implantable defibrillator. Capacitor quality and aging issues were addressed.

Premarket Support - Scientific Evaluations
Key words: electronics, forensics, regulatory support, fire, standards/guidance

OST engineers consulted on a premarket review case, involving a novel technique for securing bone staples. The staple was designed to be inserted into pre-drilled holes in the bones to be fastened. The device in question passes electrical current though the staple, causing it to become hot. The tines of the staple are designed to deflect inward when heated, permanently securing the staple and fixing the joint. OST was to assess whether UL Standard 2601-1 was adequate to assure safety of this device. It was determined that UL 2601-1 did indeed apply to this device, and that the device appeared to be compliant. However, the issue of possible tissue necrosis due to heating of the staple is a clinical issue and thus outside the scope of the standard. OST staff carefully explained the limits of applicability of the standard and suggested how the clinical issues could be clarified.

Quality Management
Key words: quality systems

An OST engineer has worked with senior CDRH management to begin implementing a Center-wide quality plan. OST has advocated applying the concepts of design control, quality systems, and risk management to a variety of regulatory problems. Positive impact by OST on the direction and outcome of several reengineering efforts, on the science review, and on several premarket guidance documents has been achieved. Specific examples include the following:

- A *tutorial* was presented on the principles of design control in the Staff College Quality Lecture series. Part of this presentation focused on the need for organizations to develop an integrated system of quality management processes that encompasses product quality, risk management for safety, environmental management, regulatory requirements, and business decision-making;

- *Technical support* was provided to the FDA Laboratory Accreditation Committee on a number of issues, including estimating the cost of implementation and formulating a training plan;

- A *consultation* was provided to the Office of Regulatory Affairs on implementing a document control system;

- *Consultations* were provided 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;

- *OST provided* consultation to several CDRH reengineering committees to help them to validate reengineered processes. Most notably, work with the QSIT Reengineering Team has helped to ensure broad acceptance of the Quality System Inspection technique; *and*

- *Design control concepts* were incorporated into a new guidance document covering home uterine activity monitors. This guidance document describes a means by which manufacturers can establish substantial equivalence to a predicate device. Designating this guidance document as a "special control," in the language of the Safe Medical Device Act of 1990, permitted home uterine activity monitors to be downgraded from Class III to Class II. By following the guidance, manufacturers can minimize the effort required to prepare the premarket submission and significantly streamline the Agency's review. In response to this request for assistance, OST developed plain language clarifying the distinction between a premarket review of design information and a quality system review of the same or similar information. Now that design controls are firmly ensconced in the quality system inspection, premarket reviewers may avoid covering the same ground as covered by quality system investigators.

Additionally, OST engineers led an effort to lay the groundwork for a quality management system within the Office of Science and Technology. This included preliminary training for managers in quality management system concepts, performing a gap analysis to assess the degree to which the Office's existing management systems satisfy the requirements of ISO 9001, and developing a detailed plan and cost estimate to implement a compliant quality management system.

Risk Management
Key words: risk management, training

OST developed a plan for training Center staff in the principles and practices of risk management, how those principles and practices are applied by device manufacturers, and how risk management information can be used to expedite the review process. This has been a major undertaking affecting ORA, OC, and ODE. First, OST staff worked with ORA in developing a set of computer-based training modules in technical risk management for field personnel. OST developed the outline for the first training module, identified CDRH experts in human factors and software hazard analysis to work on modules, and has provided an expert to write the module on risk management and the Quality System Regulation. In addition, OST participated in the ISO/IEC 14971 Joint Working Group on Risk Management for Medical Devices.

Reliability
Key words: reliability, dependability

For the past several years OST has provided the representative to the IEC TC 56 on Dependability. This work has resulted in the FDA recognition of IEC 61812 Analysis Techniques for Reliability - Failure Mode and Effects (FMEA). FMEA is the primary risk analysis technique used by medical device manufacturers, and recognition of IEC 61812 will promote harmonization in this important area with regulatory organizations in other countries. IEC TC 56 has now moved on to revising IEC 60300-3-1 on Dependability Analysis Techniques, the purpose of which is to increase its relevancy to modern dependability programs of the type used by the vast majority of medical device manufacturers. Issues in medical device reliability and dependability have pointed to the need for a new laboratory in OST concerned with issues of reliability -- a laboratory capable of analyzing data coming from a variety of sources and generated under a variety of test conditions. OST tested the concept of a Reliability Laboratory when, in support of DCRND in the review of an IDE and PMA for two Left-Ventricular Assist Devices (LVADs), it provided technical analyses of the company's reliability programs and evaluation of reliability data.

MATERIALS AND DEVICE CHARACTERIZATION

The focus of this program is to develop and assess suitable characterization methods and the generation of baseline data of the chemical, physical, and mechanical properties of medical devices and their materials. The effects of devices, drugs, radiation, etc. on the physical properties of tissue, as well as research into the determination of specific exposure limits are included in this area of study. By undertaking work in this program area, OST will help CDRH with its regulatory mission by participating in the development of consensus standards and characterization techniques that allow for the timely review of many diverse products, including absorbable sutures and vascular grafts. With OST’s extensive expertise in materials, the Office drafted standards that assist manufacturers in assessing the MRI compatibility of their devices by evaluating the potential for soft tissue damage by either torque or unbalanced linear forces in the presence of large magnetic fields. The work described below on the development of a standard methodology for the measurement of powder on gloves aided in the drafting of regulations concerning the allowable limits of powders on gloves.

Experimental Pathology: Cardiovascular Devices
Key words: pathology, valves, grafts

The objective of the experimental pathology program is to identify potential failure modes associated with the use of implantable cardiovascular devices as well as the elucidation of pathologic mechanisms responsible for their failure. Studies of explanted replacement heart valves, vascular grafts and angioplasty-injured coronary arteries are ongoing. Studies completed this year include 1) the development of experimental pathology methods for the evaluation of tissue engineered replacement heart valves and small diameter vascular grafts; 2) a morphologic study of decellularized carotid artery vascular grafts; and 3) the evaluation of a swine model to assess the preclinical safety of mechanical heart valves.

Tissue Engineered Medical Products Standards (TEMPS)

Key words: standards, tissue engineering

Division IV of ASTM F04 has established itself as the recognized leader, both nationally and internationally, in the development of TEMP standards. International liaisons have been established with other standards organizations that have expanded international involvement with the consensus process.

An important initiative is an ASTM International Symposium for Tissue Engineered Medical Products Standards to be held in Miami Beach, Florida, November 4-5, 2002, in conjunction with Committee Week and proposed as a "back-to-back" meeting with the Tissue Engineering Society International biannual meeting. The goals for the symposium are to review the technology, the use of standards, and the need for standards.

Powder Measurement on Medical Glove through the Participation in ASTM Working Group

Key words: powder measurement, powdered glove, powder-free glove

Prior to the present work, ASTM D 6124 – 97 was the standard test method for residual powder on medical gloves described as powder-less, powder-free or no powder. Due to the proposed powder limit on "powdered" gloves by FDA, there was a need to modify how larger amounts of powder were measured. The Division of Mechanics and Materials Science laboratory in OST participated in the ASTM D 11.40 round robin method development. By changing to a larger filter paper size, using the multiple fresh water washes per glove, minimizing extractions/filter, preconditioning of the filter, and agitating during the wash, a new Standard Test Method D 6124 - 00 was established. This method can be used for quantitation of powder on both powdered and powder-free gloves.

MEDICAL IMAGING EVALUATION

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 the 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. During 2000, this program contributed to the soft-copy aspects of the premarket guidance document "Information for Manufacturers Seeking Marketing Clearance of Digital Mammography System."

Digital Image Display System Evaluation
Key words: digital radiography, soft-copy display

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. Currently, the primary technologies used for the display of digital medical images are laser film printers (hardcopy) and CRT-based video monitors driven by computer-controlled digital frame buffers (softcopy). This study provides the scientific basis for regulatory decisions regarding the display subsystems of a variety of digital diagnostic imaging devices. The research will lead to a more efficient review of applications submitted for clearance to market products containing such display systems.

During FY 2000, scientists were limited to setting up display hardware and software, and establishing various display measurement capabilities. Existing display hardware and workstation software were supplemented by an additional display system and software upgrades. These elements were reconfigured to provide two dual-monitor display workstations, one of moderate resolution (1728 x 2304), and one of high resolution (2048 x 2560). Both systems were equipped with photometric calibration sensors and software produced by the manufacturers of their respective frame buffers, and both are equipped with a third-party calibration package that can provide independent verification of photometric performance. At the end of FY 2000, a scientific-grade camera and computer-controlled positioning equipment were acquired.

X-ray Physics Laboratory Studies
Key words: x-ray spectroscopy, mammographic grids

The purpose of this project is to evaluate equipment and materials used in medical radiography and in the quality assurance of medical radiography systems; and to support

OST research efforts, other Center programs, and the general radiology community, when appropriate. Conducting 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 provided technical consultations to the Office of Compliance on questions related to mammography field limitation/primary barrier and "mini C-arm" fluoroscopy systems. The Diagnostic X-ray Standard was extensively revised to address radiation safety during interventional fluoroscopy.

The medical imaging physics community has noted an increasing use of higher-voltage spectra in digital mammography. In response to publication from the University of California, Davis, of Monte Carlo calculations of mono-energetic, mammographic exposure-to-dose conversion factors for an extended range of x-ray energies, OST planned and initiated a series of spectral measurements for the three anode materials used in mammography--molybdenum, rhodium, and tungsten--at tube voltages up to 50 kVp. The measurements are being made at two field positions to allow for inclusion of the influence of the "heel effect" on patient dose in theoretical calculations.

X-ray spectroscopic measurements were employed to evaluate the performance of small-size prototype grids produced using microlithographic techniques. It is expected that such grids will soon be commercialized.

Mammographic Dosimetry Studies

Key words: mammography, dosimetry, optimized mammography system

The purpose of this project is to experimentally verify Monte Carlo predictions of the exposure-to-dose conversion factors for new x-ray sources such as rhodium anode with rhodium filter and tungsten anode with various K-edge filters. This project supports the MQSA mission to promote and maintain minimum dose levels in mammography, and may result in changes to the dose determination procedure for systems using newer x-ray source options. OST scientists began the spectral measurement program described above to extend the range of tube voltages for which experimentally measured spectra are available for the three anode materials used in mammography: molybdenum, rhodium, and tungsten. The scientists performed a small study to estimate phantom doses from the optimized mammography system for several screen-film combinations being considered as replacements for the discontinued products that had been used in earlier experiments.

Imaging System Performance Evaluation

Key words: digital radiography, flat panel detector, CCD-based x-ray imager

OST scientists are extending the quantitative assessment of dose and imaging performance from the analog to digital imaging domain. OST scientists have played a significant role in developing consensus measures of imaging performance that form the basis of the nonclinical device description now required in marketing clearance

applications for a variety of imaging devices, and they are now extending these measures to digital imaging systems. Several important measures of imaging performance that are now routinely applied to analog imaging systems are based on assumptions that are violated to one degree or another by digital systems. OST is investigating the validity of these measures for digital systems and is investigating alternate performance measures that are rigorously valid for digital systems.

In one laboratory initiative, the impact of violation of the analog-system assumptions on consensus measures for digital systems was explored through a series of computer simulations. To supplement this work, OST has acquired a flat panel digital detector for experimental verification of the simulation results. In the future, actual human observer data will be compared with predicted results, derived from quantitative measurements on the digital detector, for reading imaging phatoms. It is hoped that this work will help to bridge the gap that currently exists between subjective evaluations using imaging phantoms and objective measures of imaging performance. In the area of analog x-ray devices, OST scientists are evaluating inefficiencies in imaging performance using laboratory measurements. To address the issue of optical coupling inefficiency in the image formation process, which arises in the premarket approval of, some digital imaging devices, OST set up a lens-coupled CCD-based digital imaging system and investigated the effects of system design on overall radiation use efficiency.

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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. Preclinical experiments, clinical trials, and theoretical analysis are important to develop understanding of this technology and to anticipate 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. OST contributed a section to a CDRH guidance document on submissions for bone sonometers.

MEDICAL USES OF AND ENVIRONMENTAL EXPOSURES TO RADIATION

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.

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 activity 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 has 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 charcterizing the effects of UV radiation on skin for potential use in the regulation of products such as sunlamps, tanning booths, sunscrenns, and photosensitizing drugs. In addition, a cross agency effort to estimate the effect of exposure to ultraviolet radiation and implement efforts 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.

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.

Optimization of Accelerator Targets for Neutron Capture Therapy
Key words: cancer therapy, boron, neutrons

Boron Neutron Capture Therapy (BNCT) remains a promising investigational therapy for brain tumors, and it uses boron-10 and a neutron beam to selectively produce highly ionizing helium nuclei (alpha particles) in a tumor while only producing minimal damage to the surrounding brain tissue. A variant of BNCT, capture synovectomy, has been proposed and patented for ablation of pathological synovium in rheumatoid arthritis refractory to medical treatment. Since there is currently inadequate information about the optimal performance characteristics of devices that would be used to deliver these therapeutic neutron beams, OST has initiated a project to investigate issues of potential regulatory significance using computational modeling. OST developed a computational model of the moderator which must be placed in a fast neutron beam to slow the neutrons to therapeutic energies. Moderators of deuterium oxide, carbon, Teflon, aluminum oxide, lithium fluoride, iron fluoride and an aluminum-aluminum fluoride composite were modeled. The neutron source was a lithium accelerator target bombarded by 2.5 MeV protons. Comparisons of the computed spectra of neutrons emerging from the moderators indicates that aluminum oxide, a cheap and readily available material, gave the highest fraction of epithermal neutrons and lowest contamination by fast and thermal neutrons. OST also collaborated with a local accelerator facility that will allow experimental confirmation of these results as well as *in vitro* studies of lethality for brain tumor cells.

***In vitro* Biological Effects of Wireless Telephone Emissions**
Key words: wireless communications, cancer

Due to the continuing interest in possible adverse health effects in wireless phone users, OST developed an exposure system utilizing radio frequency (RF) radiation from wireless phones to permit investigation of some of the reported *in vitro* effects of this radiation. A series of experiments was conducted to calibrate the RF exposure system for exposure of cultured cells to radiation emitted from wireless phones and to characterize the effects of this radiation on the enzyme ornithine decarboxylase (ODC). Precision calorimetry was used to measure the amount of RF energy deposited in cultured cells for both analog and digital phone signals. Experiments were then conducted to verify reports that wireless phone radiation increased the activity of ODC, a marker for tumor promotion, in cells. Exposure to a wide range of RF power levels from wireless phones did not increase ODC activity, although at higher power levels a decrease in activity was observed. This decrease was demonstrated to be due to heating of the cells by the RF

radiation. These results are consistent with a large number of experiments conducted by OST, which did not confirm reports from other laboratories that electromagnetic fields enhance ODC activity in mammalian cells and avian embryos.

Parameters for Testing and Standardization of Skin Types and Skin Response to UV

Key words: skin, ultraviolet, UV, sunlamp

Human skin can be damaged by ultraviolet radiation (UV) from the sun, sunlamps, and medical devices. To improve public health policies in this area, FDA is actively involved in revising or developing several national and international standards. However, the current knowledge provides an inadequate scientific basis for such standards, guidelines, and policies.

At present, UV sensitivity is predicted from predisposition to sunburn and tan. Unfortunately, in many cases such predictions fail. This study is being done (in collaboration with the National Cancer Institute) to see if human sensitivity to UV can be objectively predicted using instruments and biological methods. The volunteers (110) are grouped on the basis of their skin type and racial/ethnic origin (OMB 0990-0208: American Indian or Alaska Native; Black or African American; Asian; Hispanic or Latino; Native Hawaiian or Other Pacific Islander; White.) Small areas of the skin are exposed to different UV doses. Then, at different times, instrumental measurements and biopsies are performed.

At this time, the data have been collected on 55 subjects. The results obtained following a single UV exposure show that mechanical methods can detect trends but have no predictive value. An ultrasound technique detects UV-induced changes in the structure of the skin. Optical and biological (analyses of biopsies) methods show high sensitivity and should help to modernize public health policies in the area. Such policies would help consumers to protect themselves from skin cancers and premature skin aging.

Laboratory support for a revised risk assessment of skin cancer from UV-emitting devices

Key words: skin, ultraviolet, UV, cancer, risk assessment

UV research examines the biochemical changes to skin cells and has calculated the annual and seasonal UV doses of American women and men required for relative risk assessments of UV-related health effects. This combined UV research effort allows proper usage and accurate standardization of cosmetic (tanning) and medical phototherapeutic devices. This research also allows science-based risk assessments of UV-induced skin cancers, such as the potentially fatal melanoma, caused by exposure to UV-emitting devices. Expertise supports the Center Offices OC and ODE on risk-benefit issues related to cosmetic and medical devices, such as tanning, phototherapeutic, and other UV-emitting devices (e.g., Halogen and dental lamps).

Biological Effects of Exposure to Electromagnetic Fields
Key words: CRADA, radio frequency, RF, micronucleus

In addition to the intramural research described above, OST is working with the National Toxicology Program to ensure that the need for long-term animal studies is addressed. OST also established a Cooperative Research and Development Agreement (CRADA) with the Cellular Telecommunications and Internet Association (CTIA) to provide research recommendations and research oversight for CTIA-funded studies into the health effects of radio frequency (RF) emissions from wireless phones. OST organized a meeting to obtain broad expert input and issued a detailed description of research needed to investigate the reported ability of wireless phone RF to induce the formation of micronuclei in human blood. Micronucleus formation is an indicator of effects that may be related to carcinogenesis or tumor promotion. CTIA issued a request for proposals to perform the research specified by OST.

Sunlamps and Sunbeds: Activities related to possible amendments to the Performance Standard for Sunlamp Products
Key words: performance standard, sunlamp

FDA presented five possible amendments to its Performance Standard for Sunlamp Products to TEPRSSC on June 21, 2000. The proposed changes included 1) incorporation of an exposure schedule into the Performance Standard, 2) use of a skin cancer action spectrum to determine a recommended yearly maximum exposure to ultraviolet radiation, 3) revised warning labels, 4) clarification of a manufacturer's responsibilities, and 5) requirement to place warning labels in catalogues, specification sheets and brochure. TEPRSSC requested that FDA meet with the indoor tanning industry to clarify misunderstandings about these possible amendments. That industry-FDA meeting occurred on September 13, 2000. FDA continues to work on a re-draft of its possible amendments.

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 treatment (and even diagnosis) are now routinely addressed on an outpatient basis. The result 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. In FY 2000, OST investigated a number of high-priority**,** minimally invasive technologies in order to assist Center reviewers in the timely assessment of manufacturers' submissions of these pioneering products. Included in these technologies are 1) diffuse reflectance

spectroscopy for optical diagnosis; 2) optical fibers, waveguides, and endoscopes for treatment; 3) thermal ablation using radio-frequency energy; and 4) ultrasound for imaging-based diagnosis and transdermal treatment. OST's investigations centered on clarifying the mechanisms of interaction of the technology with the body and on developing meaningful measurement and test methods. OST's active involvement in these areas of high future regulatory activity have kept it in the lead during a series of discussion with the Society of Vascular Interventional Radiologists over new-technology issues. Additionally, OST's expertise in diagnostic ultrasound power measurement is such that virtually all diagnostic submissions are reviewed for dosimetric acceptability by OST scientists. This program also contributed to the development of guidance on minimally invasive optical diagnostic devices, provided consultation on the issue of cyanide production from laser ablation of uric acid stones, and contributed to reviews of device applications including fluorescence diagnostic devices and a blood irradiator. Substantial input was also provided for the development of a FDA website on LASIK. Finally, OST has established an interagency agreement with the NIH to study the application of radio-frequency thermal ablation techniques for the treatment of cancerous liver tumors. Through this arrangement, OST answered some of the critical issues in pre-market applications for ablation devices used for the treatment of soft-tissue tumors and in endometrial ablation procedures.

Determination of Tissue Properties Using Minimally Invasive Optical Techniques
Key words: tissue spectroscopy, optical disease diagnosis

This project is designed to evaluate instrumentation and techniques to deduce the optical properties of tissue over a broad spectral range. The equipment and methodology under study are expected to provide data on tissue properties to distinguish changing metabolic conditions or to identify disease. The ability to map the spectral and temporal changes in tissue optical properties is anticipated to have significant advantages over current diagnostic means. This methodology will also aid the characterization of tissue response to optical exposure, which can be used to assist in determining appropriate exposure standards for internal organs. During FY 2000, optical probes for delivering light to, and collecting light from, the target tissue were designed and analyzed. Methods have also been devised to prepare and evaluate phantoms to simulate tissue. OST is currently working to validate the optical properties of the phantoms and then assess the correlation of experimental spatial distribution measurements with Monte Carlo modeling computations.

Determination of Bone Density Using Minimally Invasive Optical Techniques
Key words: bone density, optical spectroscopy

Work was initiated to characterize bone density using near-infrared optical radiation. Initial studies will include development of bone tissue phantoms that have optical properties resembling those of bone. The figure below shows results from a section of

swine shinbone cut on the long axis to a thickness of 0.06 cm and measured in a Shimadzu spectrophotometer fitted with an integrating sphere. Reflectance and transmittance values thus obtained were analyzed using the Inverse Adding Doubling program developed at the University of Oregon. The values shown in the figure below for wavelengths below 650 nm compare favorably to literature values.

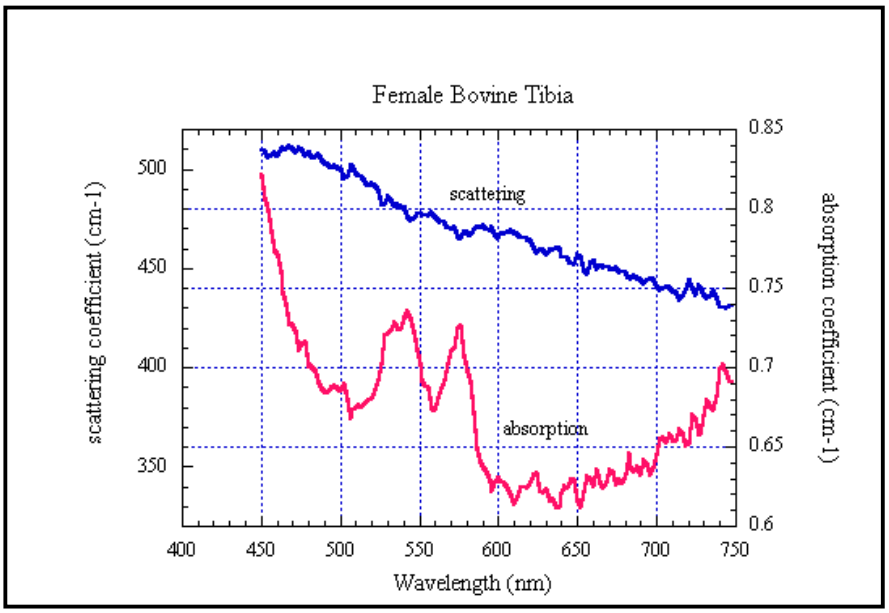

Figure 5

Evaluation of Endoscopes Used in Minimally Invasive Diagnostic and Therapeutic Procedures

Key words: endoscopes, optical radiation, minimally invasive diagnostics

This project is designed to characterize the optical radiation emissions from endoscopes used in various minimally invasive diagnostic and therapeutic procedures. The data obtained to date indicate that most endoscopes emit relatively little ultraviolet radiation below a wavelength of 370 nm and have greatly attenuated emissions at infrared wavelengths greater than 700 nm. In order to obtain a more comprehensive survey, more devices will be tested in FY 2001. When a variety of endoscopes have been measured, the results will provide CDRH with independent data to be used in developing reviewer guidance documents and will be used as a benchmark for evaluating the optical radiation safety of new endoscopic devices.

Fibers and Waveguides Used for Minimally Invasive Surgery

Key words: optical fibers, fiber transmission

Using funding obtained via an interagency agreement with the Armed Forces Office of Scientific Research, work continued on the testing of infrared fiber optics, ultraviolet

optics and x-ray optics designed for medical use. OST continued to evaluate tapered hollow glass tubing for radiation transmission in the ultraviolet and x-ray spectral regions. Tapers have proved valuable for their ability to homogenize the laser beam profile, allowing delivery of uniform energy profiles to phantom materials and tissues. The use of optical fibers with evanescent fiber tips allow laser energy to be accurately delivered to a tissue surface while avoiding the exposure of surrounding tissue. OST has also evaluated selected fiber optics components for use in a confocal imaging system. These instruments could be designed to provide more finely detailed images of tissue through fiber imaging systems used with conventional endoscopes. Data obtained from these studies will develop expertise that will be useful in evaluating optical fiber delivery systems used with medical devices.

Therapeutic Laser Devices Used for Tissue Ablation

Key words: angina, laser therapy, heart disease

Two recently developed procedures for minimally invasive treatment of angina are the subject of intense clinical investigation: transmyocardial laser revascularization (TMR) and percutaneous laser myocardial revascularization (PMR). These procedures use lasers to cut channels in a beating heart to relieve the symptoms of angina. Two recent PMR clinical studies have shown that the mechanism(s) responsible for a therapeutic effect remain in question. Other studies indicate that two mechanisms, angiogenesis and denervation, play a major role in the relief of angina. Both of these latter two mechanisms depend upon the amount of tissue damage that occurs during laser channel formation in the myocardium. OST has initiated a laboratory study to provide data to support developing review guidelines for TMR and PMR. The effort is focusing on laser-tissue ablation performance, as well as acoustic-mechanical performance. These studies will be carried out in a phantom material, polyacrylamide gel. Polyacrylamide gels have been used to study the performance of one of the common lasers, the Ho:YAG laser, that has been used in the clinical studies.

Heat Transfer Issues in Catheter Ablation Devices

Key words: ablation, heat transfer radio frequency

This project is devoted to studying how heat is generated and dissipated in medical devices that use radio-frequency energy sources to destroy (ablate) diseased tissues. OST is one of the few groups examining the physics of ablation in *in vitro* experimental systems and with computer simulation models. The main objectives of this project are to develop new tools for evaluating ablation devices, to research the physics of the ablation process, and to develop appropriate safety and efficacy guidelines for cardiac arrhythmia and liver tumor ablation devices. OST scientists have developed a new test system that uses both solid and liquid versions of blood and soft tissue-simulating materials with the same electrical properties as real tissues. The system uses laser instrumentation to measure temperature distributions in the tissue-simulating materials during radiofrequency heating with blood flow. This system has been used to manipulate the various parameters affecting the ablation process.

Measurement of Laser-Induced Acoustic Stresses

Key words: Laser-tissue interaction, optical fiber, laser-induced stress, Er:YAG laser

Er:YAG lasers are being studied as candidates for surgical procedures in liquid environments, such as in ophthalmology. For example, the small tissue penetration depth (a few micrometers) along with minimal thermal damage makes the Er:YAG laser an appealing candidate for the removal of epiretinal membranes in vitrectomy. However, the strong absorption that makes the Er:YAG laser such a precise cutting tool is also responsible for thermoelastic and collapse-induced stress transients that must be quantified and evaluated for potential harm. Therefore, OST scientists in collaboration with the Department of Biomedical Engineering at Tel Aviv University have begun a study of Er:YAG laser-induced stress waves. Using a high-fidelity acoustic pressure sensor constructed by OST engineers, measurements were acquired beneath a biological membrane submerged in a saline bath. Results yielded pressures peaks of 300-600 mbar beneath the uncut membrane, which could be harmful for the optic nerve if located directly below the treatment area. Acoustic waves representative of direct laser-liquid interactions were observed immediately following membrane rupture and yielded much larger pressures. These morphological changes in the acoustic wave could be used as a feedback signal to indicate when the membrane has been cut. OST will continue to study potential acoustic damage to the delicate structures of the eye because of the increasing use of lasers for many types of eye surgery. For example, acoustic damage to the cornea's endothelial cells could lead to long-term problems as the eye ages.

PHYSIOLOGICAL SIGNAL ACQUISITION, ANALYSIS, AND CONTROL SYSTEMS

The signal acquisition system of a medical device is the electronic circuitry and control processor that receives, as inputs, signals from biological, chemical, mechanical, or electric-field sensors that are within or attached to the human body. These signals are processed in subsequent decision-making circuitry within the device. The interpreted signal can be used as a monitor or warning signal or to control a responding mechanism. Examples include cochlear implants, fetal oximetry, and home uterine activity monitors. The fidelity with which a physiologic signal is captured is often critical to the overall performance of a medical device. In FY 2000, OST participated in over 40 IDE, PMA, and 510(k) reviews, for devices including cochlear implants, pacemakers, fetal oximeters, implantable defibrillators, gas analyzers, ventilator support systems, apnea monitors, and resuscitators, where the signal acquisition system and associated electronics were the subject of the review.

Laboratory Design/Staff Development
Key words: signal acquisition, 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 2000, much of the infrastructure for this system was developed and the first of the new controllers, the shutter controller, was deployed on both the main radiography and the mammography x-ray systems.

OST's Division of Physical Sciences (DPS) developed a course in biomedical engineering for the CDRH Staff College. The course consisted of eight lectures, each with an associated case study. An OST engineer developed two of the eight case studies, covering analog amplifiers and data acquisition principles. The goal of the training was to relate the concepts of biomedical engineering to real-world regulatory issues.

PREDICTION OF MATERIALS STABILITY AND IDENTIFICATION OF DEGRADATION MECHANISMS

This program 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 the identification of critical parameters, either in the device fabrication history or in the service environment, which can lead to failure through material related causes. These service environments can be as varied as site of implantation, application conditions (oxygen rich atmospheres for example), or storage conditions of devices and components. 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.

Abrasion Resistance of Medical Glove Materials
Key words: gloves, abrasion resistance, tear strength

With an increasing demand for non-latex medical gloves, there is a need to assess the durability of alternative glove materials. The durability characteristics of specimens cut from the back and palm area of five varieties of medical gloves were explored via abrasion resistance to a smooth, stainless steel abrading bar. The five glove materials evaluated included natural rubber latex and four non-latex alternatives: nitrile, neoprene, vinyl, and a styrene-ethylene/butylene-styrene block copolymer ("SEBS"). Most specimens were obtained from surgical gloves except for vinyl specimens that were obtained from examination gloves. Results indicated that abrasion resistance is dependent on glove material and not necessarily on thickness of the material.

The Body's Response to Deliberate Implants: Phagocytic Cell Responses to Large Substrata versus Small Particles

Key words: biocompatibility, cell spreading, implants

It is important to characterize possible inflammatory responses to small particles and to clearly separate these effects from responses to larger objects nearby. This research monitors the intermediate production of inflammation-related reactive oxygen and morphological alterations of human monocyte-derived macrophages interacting with the walls of nonpolar and polar polystyrene cuvettes and with small particles of Teflon, polyethylene, Co-Cr-Mo alloy, titanium and alumina. The two types of polystyrene substrata represent the nonpolar "bacterial" (as produced) and the polar "tissue culture" (gas plasma treated) materials widely used in biological testing. The spreading of macrophage during contact with the higher surface energy, polar substratum further suppressed "oxidative bursts" than from rounded cells in contact with the lower-energy, non-polar substratum. Particulate matter engulfed by both rounded and spread cells did not significantly enhance intermediate oxygen production beyond levels observed for no-particle controls. Biocompatibility of some implants might be related to cell-spreading, induced suppression of reactive oxygen intermediate production, improving the tissue integration of gas plasma treated implants.

Cleaning and Performance of Single Use Devices Project

Key words: single use, resterilization, gastrointestinal devices, cleaning protocols

OST continues studies on the effects of reprocessing single use devices for interventional cardiology and gastrointestinal procedures continue. Material and degradation studies focused on developing a variety of mechanical and chemical characterization methods. Interventional cardiology devices were subjected to repeated resterilization with ethylene oxide to study the effect on balloon compliance and catheter resistance to twisting and bending. Evidence of chemical degradation was also investigated with FTIR. Corrosion test methods were utilized to examine the effects of material composition and device design on degradation of metallic components of gastrointestinal devices. Scientists examined microstructural and chemical compositional changes by scanning electron microscopy and x-ray analysis. These methods were also used in developing a protocol for chemically tagging various biological soils for the microscopic examination of the effectiveness of cleaning protocols.

Use of Physiologically-Based Pharmacokinetic Models (PBPK) in Risk Assessment
Key words: PBPK, risk assessment, D4

PBPK models provide a physiological representation of the biological system and describe the relationship between exposure and system responses leading to adverse health effects. Predicting tissue doses or accumulations as a function of exposure indicates where adverse effects would occur, as most are proportional to dose. Because the PBPK model incorporates physiological, biochemical information specific to the chemical as well as to the species tested (animal or human), it offers a method to extrapolate from high to low doses, one route to another, and especially from one species to another. This reduces uncertainty compared to risk assessments based only on exposure levels. Recent PBPK models developed in OST have predicted bioaccumulation of octamethylcyclotetrasiloxane (D_4) in fatty tissues (e.g. breasts), the absorption, distribution, metabolism, and excretion (ADME) of toluene diamine from polyurethane implants, and the ADME of methylene dianiline leached from hemodialyzers.

An *In-Vitro* Study of the Effect of In-Folds on Durability of Mammary Implants
Key words: mammary implant, fatigue, *in vitro* testing, silicone polymer.

This project examined whether the presence of an "in-folding" in a filled mammary shell could lead to shortening of the time-to-failure, under tensile fatigue. Specimens, cut from pristine shells, were prepared and mounted in `S'-folded, creased and unfolded configurations. A characteristic change occurring in a transmembrane capacitance AC signal, used to monitor working of each specimen, was chosen as a marker that preceded frank shell perforation. Subjecting all specimens to controlled conditions led to estimates of time-to-failure that demonstrated an order-of-magnitude reduction in typical lifetime for the folded specimens, when compared with that for pair-matched, unfolded specimens. Creases also reduced the fatigue lifetime but not as much as folds. Observations based on the experimental behavior of folded shell material have provided possible mechanisms for the development of in-folds clinically, as well as for the development of silicone-on-silicone abrasive wear and generation of debris.

Shelf-Life of Non-Latex Condoms
Key words: shelf life, condoms, mechanical properties

Assessing the shelf life of these products is important because generally a long shelf life is desired. Various environmental agents, lubricants, and additives may affect the shelf life of condoms made of new materials where a history of use has not been well established. OST has studied the effect of various solutions of the spermicide nonoxynol-9 in polyethylene glycol on the properties of various polyetherurethanes used to make condoms. Breaking strength was inversely proportional to the concentration of nonoxynol-9, but stretching the material to failure did not show any trend. Mass uptake and swelling occurred in the first 20 hours of exposure and then approach limiting values.

Most effects showed a variation with the orientation referring to the roll direction for films. Adjusting the initial mechanical properties to allow for some decrease by the additives is likely to be sufficient.

Shelf-Life of Medical Gloves
Key words: shelf life, gloves, accelerated test

Manufacturers desire to have an accelerated test to establish a tentative shelf life before all the real data is acquired. Studies of temperature aging on latex glove fingers are underway in an effort to better understand the process and thus determine the acceptability of various accelerated tests. Creep and modulus are measured under forces comparable to those developed during actual use. Their behavior in short-term tests at higher temperatures is different from that in longer-term, low-temperature tests. This may explain why attempts to use the Arrhenius or the Q_{10} relationship with latex materials do not work very well. OST has been working with an ASTM D11:40 glove subcommittee on developing acceptable accelerated tests.

Shelf-Life of Cellulose Acetate Hemodialyzers
Key words: cellulose acetate, degradation, simulation

A previous investigation in an OST laboratory linked cellulose acetate (CA) membrane degradation with adverse health effects in hemodialysis patients. A molecular population model was developed to track CA degradation of a dialyzer membrane during storage. The model used a random number to select individual polymer molecules out of a population, and then another to select a site on the molecule for the degradation reaction to occur. The resulting molecular fragments were then redistributed into the population. Molecular weight averages and acetyl content were recalculated as the reaction simulation proceeded. The model was validated with experimental measurements, including the molecular weight distribution, on dialyzers stored up to 13.3 years. It was found that the degradation reactions can be accurately modeled as random events and that the reaction events occur at constant rates.

RADIATION SAFETY

Radiation safety continues to be a significant concern for the Center. To help CDRH address this topic in FY 2000, OST maintained its calibration facilities for both laser and microwave measurements. In addition, OST continued to investigate the deleterious effects of UV radiation on the skin and retinal hazards from ophthalmic instruments. This program provided laboratory data and consultation aimed at the revision of the CDRH Sunlamp Performance Standard, the CDRH Laser Performance Standard, the CDER Sunscreen Monograph, and the development of ISO standards on Ophthalmic Instruments and various aspects

of laser safety. In addition, the program provided laboratory measurements and calibrations of light meters and laser measurement instrumentation for field enforcement of FDA performance standards. It also provided product evaluations on laser pointers, laser range finders, and night vision instruments, and contributed to center-wide working groups on radiological health reengineering.

Ophthalmic Instruments – Fundus Cameras
Key words: fundus cameras, ophthalmic standards

OST initiated work to study the potential optical radiation hazards associated with the use of fundus cameras to obtain photographs of the retina. OST instrumentation was assembled to measure the integrated spectral radiance of the light emitted from the pulsed Xenon sources used in these devices. Preliminary data showed relatively little ultraviolet and infrared radiation emissions from the device tested. More testing is planned for FY 2001. These independent data will be used to develop major amendments to the ISO 15004 Ophthalmic Instruments Standard.

Ultrasonic Characterization of Skin Following Ultraviolet Light Exposures
Key words: photodamage, dermis, Minimal Erythema Dose (MED), high-frequency ultrasound imaging

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 (20MHz) ultrasound imaging to measure changes in skin structure after exposure to UV radiation. Scientists took M measurements from 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 both the dermal thickness and ultrasound attenuation properties of the skin. These 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.

Laser Field Compliance Program
Key words: lasers, calibrations, product testing, technical support

OST continues to participate in the Center's laser field compliance program. The OST Laser Calibration Laboratory maintains equipment for conducting high precision optical measurements that provide validity to measurements taken in compliance testing programs nationwide. Periodic inter-comparisons are conducted with the National

Institute of Standards and Technology (NIST), and in-house quality assurance procedures are followed. During CY 2000, inter-comparisons were conducted with NIST at several laser wavelengths: 632.8 nm, 488 nm, 514 nm, and 1,064 nm. OST also planned and hosted laboratory instruction sessions for FDA field inspectors and personnel from the Office of Compliance. Several pulsed laser pointers and range finders were evaluated in FY 2000 to confirm the manufacturer's classification of the products.

Microwave Oven Leakage Instrument Calibration
Key words: microwave ovens, instrument calibrations, precision, leakage, radiation

More then 30 microwave leakage survey instruments were calibrated in OST's Electrophysics Branch Precision Anechoic Chamber prior to moving the calibration facility and instrumentation to a new OST laboratory building. This work is done in support of the microwave oven performance standard that limits leakage from these consumer and industrial radiation-emitting products. OST began converting an existing shielded room in the new OST building into an anechoic calibration chamber for precision microwave instrument calibration. The chamber design and instrument positioning equipment were designed and specified in a contract that was awarded to construct the anechoic chamber.

Laser Performance Standard
Key words: lasers, standards, harmonization

OST participated in the Center's effort to amend the FDA performance standard for laser products to bring it into closer harmonization with the international standard issued by the International Electrotechnical Commission (IEC) [IEC 60825-1]. OST also participates in voluntary standards activities by serving on the ANSI Z136.4 (laser measurements) committee. In the international arena, OST is participating on the ISO TC172/SC9 subcommittee, where work continues on modifying the ISO standards for determining the laser resistance of the shafts of tracheal tubes, laser resistance of surgical drapes, and patient protective covers. OST also hosted a meeting of the U.S. members of the project group.

Sunlamp Performance Standard
Key words: sunlamps, standards, harmonization

OST is participating in an effort to revise the FDA Performance Standard for Sunlamp Products to harmonize with the International Electrotechnical Commission (IEC) 335-2-27 Standard, which includes criteria for skin exposure to ultraviolet radiation. The IEC intends to incorporate a maximum timer limit for sunlamp products, similar to the current FDA requirement. The current FDA requirement is being modified so that the value of MED, which the timer limit is based on, is increased to a value more consistent with recent scientific data. OST performed laboratory measurements to provide independent data to justify changing the MED value. In addition, OST worked with the Winchester

Engineering and Analytical Center (WEAC) to analyze spectral transmittance data of protective eyewear for ocular hazards in order to develop new transmittance limits that protect the eye while undergoing sunlamp exposures.

CDER Sunscreen Monograph
Key words: sunscreens, standards, ultraviolet radiation

FDA/CDER is preparing to modify the current Sunscreen Testing Monograph to include provisions for UVA protection. OST performed *in vitro* testing of the UVA absorbance of several types of commercially available sunscreen products. The results of this testing provided independent data to demonstrate that currently used *in vitro* test methods lead to large variability in predicted product performance, mostly due to the fact that the substrate used in the testing does not mimic human skin. As a result of these findings, FDA is reconsidering requirements for *in vivo* testing of UVA transmission of sunscreen products.

REUSE/STERILIZATION/DISINFECTION/INFECTIOUS DISEASE DIAGNOSTICS

Key words: preclinical, biocompatibility, materials science, sterility, reuse, clinical use, surveillance, risk analysis, end of product life, infectious diseases, *in vitro* 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 were intended as single-use devices (SUD's). 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 the regulations. The experience gained from this program will allow CDRH to understand the problems and ask the right questions related to SUD reprocessing. SUD's were intended by the original equipment manufacturer (OEM) to be discarded after single use and not to be reused on another patient. SUD's 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. SUD's 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, cardiac ablators of various kinds, ultrasonic imaging catheters, angiography catheters, guiding catheters, revascularization catheters, and balloon catheters for wedge procedures. Each device has its own specific cleaning needs and various materials are used. The gastrointestinal devices include various models of GI biopsy forceps and snares, devices for retrieving gallstones (balloons, snares, ERCP devices), and various GI catheters.

Protocols for cleaning, sterilizing and evaluating performance of these devices are being developed. These studies provide independent data to support review and regulatory decision-making related to the adequacy of reprocessing of SUDs. This research is designed to uncover problems that the reprocessor may inadvertently run into while reprocessing single-use devices and that CDRH needs to be aware of in regulating the practice of reprocessing single use devices. 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 industry. However, newer technologies are also being incorporated to understand important advancements that must be considered for managing risks in the future.

This program has contributed independent data and information that is being used in compliance actions and in device approval considerations. The output from this research played a major role in formulating the CDRH policy that, effective February 14, 2001, third party reprocessors and hospitals must follow. All third party reprocessors had to submit PMA applications for reprocessing Class III devices by February 14, 2001, and must submit 510K applications for other devices by August 14, 2001. The hospitals have until the August date to submit PMA or 510K applications. The research team is active in reviewing these documents. The research team is also actively participating in developing standards for cleaning methods/validation and issues of sterilization.

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 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 3) efficiently standardize the associated methodology.

Cleaning and Performance of Single-Use Devices

Key words: reuse of single use devices, cleaning, simulated soils, preclinical

OST continued to study the effects of reprocessing single-use devices for interventional cardiology and gastrointestinal procedures. Cleaning these devices indicated unique problems with access to lumens and interstices containing blood and tissue. This was of special concern in some of the newly acquired devices with lumens that were difficult to recognize, contaminated with biological material, and not accessible for cleaning. Changes in the devices and the presence of lumens are not trivial in developing cleaning protocols. A tenacious soil to simulate biological debris, and which can be introduced into narrow lumens, was developed to validate cleaning protocols. The effect on device performance and materials properties after simulated reuse and cleaning of such soil is leading to new technologies and issues to be addressed in reprocessing.

Standards for Sterilization and Cleaning Methods

Key words: standards, sterilization, cleaning, disinfection, AAMI

OST is involved in writing, reviewing, and approving various national and international standards. "Sterilization of medical devices-requirements for products labeled 'Sterile'" was finally approved. OST is involved in writing "Bacterial endotoxin-test methodologies, routine monitoring and alternatives to batch testing." Additionally, a new work proposal "Compendium of cleaning reusable medical devices for reprocessing was submitted to the Association for the Advancement of Medical Instrumentation (AAMI). OST staff are involved in AAMI Sterilization Standards Committee/U.S. Technical Advisory Group (TAG)for ISO/TC 198, Sterilization of health care products as members of various working groups (Executive Board, Co-chair of AAMI Sterilization Standards Working Groups/U.S. Sub-TAGs, Microbiological methods, Sterilization Packaging, Decontamination, Washer-Disinfectors, Cleaning).

Developing a PCR-PNA-ELISA Procedure for Rapid Detection of Antibiotic Resistant Strains of Mycobacterium Tuberculosis (MTB)

Key words: Mycobacterium tuberculosis, *in vitro* diagnostics, polymerase chain reaction, PCR, peptide nucleic acid, PNA, standard.

The emergence of drug-resistant strains of *Mycobacterium tuberculosis* (MTB) remains a serious public health problem. New methods for the rapid diagnosis of MTB drug resistant strains are needed. OST is developing a polymerase chain reaction (PCR)-peptide nucleic acid (PNA)-based ELISA as a diagnostic method using point mutations in genes associated with isoniazid and rifampin resistance in MTB. PCR with fluorescein-labeled primers is used to amplify specific regions of the mutant or wild-type cloned mycobacterial genes. Biotinylated PNAs bound to streptavidin-precoated microtiter wells are incubated with the (denatured) PCR-amplified mutant or wild-type gene sequences under conditions that allow hybridization to occur between the labeled PNAs and amplified DNA.

After hybridization, color (405 nm) is developed following addition of an anti-fluorescein conjugate and appropriate substrate. Thus far, OST scientists have established the hybridization temperatures (50-55^{o}C) and other experimental conditions suitable for detecting a number of clinically relevant point mutations in the katG and rpoB genes, using PNA containing 15 bases DNA probes. Hybridization of PCR-amplified MTB DNA sequences that contain these point mutations with mutant-specific complementary PNAs result in ~ 6-10 fold increases in ELISA response compared to hybridization using MTB wild-type-specific PNAs. Conversely, wild-type MTB sequences hybridize more efficiently at 50-55^{o}C with wild-type PNAs than with the mutant-specific PNAs. Using the PCR-PNA-ELISA method with these MTB drug-resistant gene model systems, scientists can identify drug-resistant MTB sequences in less than 24 hrs.

During the course of this work, the OST Project Principal Investigator led the development of an important standards guideline. The guideline (E2048 "Standard Guide for Detection of Nucleic Acids of the Mycobacterium Tuberculosis Complex and Other Pathogenic Mycobacteria by the Polymerase Chain Reaction Technique") was developed through ASTM Committee E-48 on Biotechnology in collaboration with DIN (Deutsches Institut fuer Normung = German Institute for Standardization) Committee E3/E9 on Molecular Biological Detection of Mycobacteria. This guideline was published by ASTM in January 2000.

Isolation of High Molecular Weight DNA from Human Brain Tissue
Key words: DNA, DNA isolation, brain, polymerase chain reaction, PCR

A method was developed for the cold-temperature isolation of high-molecular weight DNA from postmortem human brain tissue. Brain tissue samples were taken from different locations of three brains and frozen at -70^{o}C. Small portions of each sample were immersed in liquid nitrogen and ground to a fine powder with mortar and pestle. The powder was allowed to thaw in buffer and then quickly treated with a protein-digesting enzyme followed by standard phenol-chloroform extraction of DNA. Since the extracted and pulverized brain tissues are kept frozen as long as possible before DNA isolation, there is less chance that DNA degradation can occur. The isolated DNA was analyzed by spectrophotometry and shown by agarose gel electrophoresis to be of high molecular weight. The presence of DNA in the isolated samples was also demonstrated by amplifying a segment of the β-actin gene from an aliquot of the preparation by polymerase chain reaction (PCR) using specific primers.

This procedure was developed during a previous investigation that concerned the use of PCR to determine the distribution of HIV-genomic DNA in brains of deceased AIDS patients at different stages of HIV infection. Developing methodology was a collaboration with investigators from the Institute of Molecular Virology, GSF National Research Center for Environment and Health, Neuherberg, Germany. This brain DNA isolation procedure could be useful for PCR studies that require high-molecular weight brain DNA as starting material. An example of such study is the performance of PCR or

other DNA-based molecular *in vitro* diagnostics procedure to determine the extent of central nervous system infection associated with epidemics caused by DNA-containing microorganisms.

The development of a guideline ("Standard Guide for Detection of Nucleic Acid Sequences of the Human Immunodeficiency Virus HIV-1 by the Polymerase Chain Reaction Technique") was associated with this project. This project was led by the OST Project Principal Investigator through ASTM Committee E-48 on Biotechnology in collaboration with DIN (Deutsches Institut fuer Normung = German Institute for Standardization) Committee E9 on Serodiagnosis of Infectious Diseases and Diseases of the Immune System. The guideline is currently up for vote within ASTM for approval.

SOFTWARE ENGINEERING

OST provides software support for the Center's premarket and postmarket activities by concentrating on the most critical steps in the process of developing and marketing safe software. These areas are Software Safety and Software Risk Management; Software Requirements, Analysis, and Definitions; Software Design Methods; and Software Verification, Validation, and Testing. Tools intended to assist software developers in each of these areas are evaluated and tested. Demonstration projects are developed in order to arrive at metrics for the various tools, and the results are infused into the regulatory process through standards, training, publications, and guidelines. OST participated in over 100 IDE, PMA, and 510(k) reviews where software was the subject. The medical devices included pediatric and adult cochlear implants, LSX, VISX, and excimer lasers, pacemakers, breast cancer scanners, bone densitometers, thermal imaging, CADx systems, labor assistors, implantable pumps, brainstem implants, radiation therapy systems, sterilizers, disinfectant systems, wheelchairs, and linear accelerators. In addition, OST provides software engineering services to ORA by assisting in field investigations, to FDA for developing policy related to Part 11 - Electronic Records and Signature, to CDER for bioresearch monitoring and clinical trials software, and to CBER in developing the Bloodbank Software Reviewers Guidance.

Y2K Issue

Key words: software, regulatory support, Y2K

In FY 2000, OST was involved in the Y2K issue to a high degree, at several levels. At the policy level, OST provided the FDA focal point to the President's Council on Y2K Issues and technical and administrative support for this representative. As spokesperson for the FDA and with the technical support of many OST engineers, the OST

representative was able to steer FDA onto a science-based approach to the Y2K problem: an approach that resulted in an effective solution without an undue waste of resources in reaction to overstated perceived threats. He was supported by sound technical information provided by OST engineers, and he was able to define the problem and work with the FDA Commissioner and her staff, with representatives of the White House and of Congress, with members of the medical device industry, and with technical specialists throughout FDA to achieve an effective solution to the Y2K crisis.

At the operational level, OST provided a technical representative to each of the three triage teams in OSB. These teams reviewed and acted on all reports of Y2K non-compliance in medical devices. OST staff also drafted the Statement of Work for a contract audit of the Y2K programs in a sampling of medical device companies. OST reviewed the technical qualifications of potential contractors for this audit. The audit was performed and successfully predicted that the industry was sufficiently prepared for the transition to Year 2000 so that drastic steps on the part of the FDA were not warranted.

Determining Best Practices and Establishing CDRH Software Policy
Key words: software, standards, policy

The Y2K Bug "scare" served to highlight the potential consequences that defective software could cause in medical devices. As a result, the Center decided to rethink how medical device software was regulated. Under the leadership of OST software engineers, the Center took several steps to identify and apply existing best practices in assuring software reliability to the regulation of medical device software.

OST has lead a joint FDA/industry effort to develop a software safety standard specifically tailored for medical devices by providing the co-chair for the AAMI Software Committee. This group has successfully developed a Medical Device Software Engineering Life Cycle Standard. The draft standard has been submitted to the AAMI and ANSI standards board and is expected to become a U.S. National Standard in June 2001. Once finalized, this standard can be used by the developer of any low- and moderate-risk medical device software. The conformance to this standard will enable manufacturers to submit less premarket software documentation, thereby reducing CDRH workload in reviewing medical device software applications and speeding up time to market for the device.

At the urging of OST engineers, the AAMI Software Committee has initiated an effort to develop a Technical Report on Software Hazard Management. The purpose of this Technical Information Report (TIR) is to provide a consensus reference document that encapsulates the application of the Software Engineering Body of Knowledge to medical device software hazard management. OST is providing the co-chair for this effort.

An OST software engineer represents FDA on the Defense Advanced Research Projects Agency (DARPA) High-Confidence System Workgroup. This is a government-wide committee charged with analyzing and funding research on engineering methods for

safer, more secure and more reliable software. FDA provides input concerning public health issues to this forum. This engineering input fosters improvement in the state of the art of software development, which provides manufacturers with the tools necessary to produce safe and effective software.

OST engineers have provided software engineering technical expertise to the FDA Part 11 Committee. The Part 11 Committee is charged with implementation of the Part 11 regulation on Electronic Records and Signature as well as the writing of guidance on various Part 11 topics. OST engineers provide the committee with engineering and design review services.

OST has lead an effort to include software engineering concerns in the proposed revision of the Medical Electrical Equipment Safety Standard IEC 60601-1. Working through the Center's Software STG, comments were collected and consensus was reached on the Center's positions on many key issues. Fifteen pages of comments were submitted for the Standard Committee's consideration. These software engineering concerns are based on the requirements of U.S. Food and Drug law. The effort will contribute greatly to the harmonization of regulated medical device software.

Implementation of CDRH Software Policy

Key words: software, training, policy, outreach

As the CDRH Software Policy is being developed, implementation of this policy is also beginning. OST engineers are currently participating in three software educational outreach programs. OST engineers are discussing the new policy in open meetings, are providing training both in-house and extramurally, and are producing technical papers that discuss the foundations of the new policy.

OST software engineers co-designed a medical device software engineering seminar that is currently being taught at the University of California, Irvine. OST software engineers are currently working with AAMI to develop a course on software validation that is scheduled to debut in fall 2001. In addition, the software team is preparing to deliver software engineering workshop at the University of Minnesota in July 2001.

For the second year in a row, OST engineers organized and directed a software engineering session at the annual AAMI Standards Conference. OST engineers used their leveraging power and their engineering skills to arrange for six different speakers to contribute to continue educating industry on the use of standards in the development of safe and effective software.

OST prepared and presented to ODE reviewers a six-session training course covering Software Requirements, Hazard Analysis, Standards, and Verification, Validation, and Testing.

An OST engineer co-authored the article "Engineering in Software Testing: Statistical Testing Based on a Usage Model Applied to Medical Device Development" which appeared in the July/August 1999 issue of the AAMI Biomedical Instrumentation & Technology Journal. The article presented the theory behind the concept of applying usage models in developing and testing high reliability software for medical devices. The article, although contributing to advancing knowledge in this area, is of limited practical use to the small software developer because it lacks particulars about how to generate the usage model. This project will ultimately serve two purposes: 1) a usage model for radiation treatment planning (RTP) software will be developed thereby assisting both companies that develop RTP software and reviewers in CDRH who evaluate the product and 2) the research will form the basis for a follow-up journal article on developing usage models. This will be a collaborative effort between ODE, OST, NEMA, and industry. The usage model will be developed using Cleanroom software engineering methodologies. It will be used to evaluate the quality of RTP software. A collateral byproduct of this work may be a NEMA standard for the testing of RTP software using usage models.

STATISTICAL ISSUES OF DIAGNOSTIC MODALITIES

This program addresses new and increasingly sophisticated computer techniques applied to medical diagnosis. These include processing of medical images or other medical data to search for signs of abnormality, with simple identification of suspicious regions for further review by a physician, or the offering of diagnostic confidence levels on abnormalities, or providing subtle quantitative physical or chemical information to the practitioner. These computerized medicine, tissue characterization, or computer-aided diagnosis (CADx) approaches use advanced statistical tools for diagnostic decision making under uncertainty, including classical Bayes' discriminants, neural-network architectures, and fuzzy logic. OST has played a significant role in device submissions that include those for automated Pap smear readers, lung cancer, and breast cancer detection devices. The computer applications program develops assessment methodologies for these systems based on the principles of statistical decision analysis.

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

Key words: computer-aided diagnosis, ROC, sensitivity, specificity

OST has previously developed a multivariate (here, six-component) statistical model for multiple-reader ROC studies of diagnostic imaging modalities. (The ROC, or receiver operating characteristic, is the graph of the trade-off between sensitivity and specificity of a diagnostic modality.) This model was applied to the design and analysis of clinical studies used during the approval process for digital mammography to account for patient

and reader variability, their interaction, and the correlation of these components across modalities, conventional and digital.

The emerging contemporary problem of comparing unaided readers (radiologists) with readers who use a computer-assist modality requires a more elaborate treatment. This year OST developed more general nine-component ROC models to accommodate this more general task. OST scientists have now analyzed a number of important academic data sets using these models and can see to what extent the computer assist modifies the reader components of variance. These new tools provide a quantitative approach to assessing diagnostic imaging modalities, computer-assists for image readers, and training radiologists. They provide the ability to design a large pivotal trial from a smaller pilot study. And for the first time, they open up an approach to modeling the marginal effects of changes in all of the above reader and computer effects as well as changes in the physical characteristics of new imaging technologies. The tools were used in analyzing a PMA for computer-assisted lung cancer detection on chest images. The adoption of these tools in the imaging community will lead to more efficient trial designs for all kinds of medical imaging modalities.

Tissue Characterization

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

This project is the application of 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 for reviewing diagnostic devices. OST continued to work 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 scientists continued their participation in developing ASTM “Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants” and AIUM (American Institute of Ultrasound in Medicine) "Performance of Ultrasonic Backscatter Measurements." They continued to collect 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. OST also developed software to compute backscatter coefficient, texture, and elastographic parameters from prostate samples.

TISSUE/MATERIAL INTERACTIONS

Key words: biocompatibility, medical device toxicology, risk assessment, standards development, methods development, laboratory research, materials toxicology, foreign body reactions

The Tissue/Material Interaction Program Area in OST encompasses an interconnected program of laboratory research, risk assessment, and standards development activities designed to provide a scientific basis for regulatory decision making in CDRH. OST remains at the forefront in developing methods for risk assessment and medical device toxicology. Information from laboratory-based research efforts are used to develop consensus standards, guidance documents, and risk assessments that form the basis of a knowledge management framework within CDRH. Specifically, OST serves as an independent source of data on medical device toxicology and risk assessment for risk managers in CDRH Offices (primarily ODE) with the primary responsibility for device evaluation.

The Division of Life Sciences laboratory research program performs experimental studies that generate independent data for use in developing standards and guidance documents. These documents provide a scientific basis for such ASTM standards as natural rubber latex protein content in gloves and condoms, for FDA guidance for the content of phthalate esters, medical grade plastics and for the assessment of the role of endotoxin in latex allergies.

Toxicity evaluation of medical device materials presents two challenges: compounds and chemicals that are released from device materials and foreign body reactions induced by medical devices and their materials. New methods are being developed to assess the adverse effects that may occur following exposure to compounds released from medical device materials and the interaction between medical device materials and cells or tissues. The scope of these studies range from short-term forensic studies (e.g., etiology of latex rubber sensitivity) to long-range mechanistic studies (e.g., effects of implant degradation and wear particles and development of more predictive molecular biomarkers). Laboratory research in this program area also addresses clinically important, high-profile issues, such as the gender differences in coronary artery response to interventional cardiology devices (e.g. balloon angioplasty catheters and cardiovascular stents) and the ability of compounds released from medical devices to have estrogenic effects. These projects underscore OST's commitment to women's health issues in this program area.

Supporting the development of standards, guidance documents, and regulations. The development of consensus standards for regulatory assessment is a core goal of the Office of Science and Technology. Both laboratory-based research and risk assessments are performed in the Tissue/Material Interaction Program to directly support the development of consensus standards, guidance documents, and regulations. For example, research conducted in OST's Division of Life Sciences to develop a method for quantifying natural rubber latex proteins served as the basis for ASTM standard D6499. OST scientists also provided the leadership role in developing a proposed rule and guidance document for medical gloves. OST experience in latex research has positioned the Center to develop

consensus from a wide and dissenting body of opinion among industry and consumers on the proper scientific and regulatory approach for tackling the problem of adverse effects associated with exposure to NRL-containing medical devices. OST's tissue engineering program has resulted in the development of a cooperative program with other Federal agencies through the MATES working group of the subcommittee on Biotechnology. In support of ODE review efforts, scientists have contributed to the review of ASTM terminology relating to tissue engineered products. Scientists have also developed draft ASTM standards on alginates for tissue engineered products.

Addressing clinically important, high profile issues in CDRH. Restenosis, or re-narrowing of coronary arteries, is a clinically important problem that occurs following balloon angioplasty. OST scientists have developed a large animal model of vascular disease that can be used to investigate the role of factors such as gender and hormonal status on the response of coronary arteries to interventional devices. An issue that has received media attention recently is the ability of certain chemical compounds to interfere with the endocrine system. One such compound that can be released from medical device materials, bisphenol A, can interfere with endogenous endocrine and hormone homeostasis. OST scientists have conducted research to characterize the estrogenic effects of bisphenol A, and this information can be used to reduce uncertainties in assessing the risk of this compound. Another issue that has received considerable media attention recently is the potential for phthalate esters used as plasticizers in PVC medical devices. OST has been assigned the lead role in the Center for assessing the human health risks posed by patient exposure to these compounds.

Addressing emerging issues and supporting the science base in CDRH. Understanding the mechanism or mode of action by which device materials or compounds released from device materials produce adverse effects is a key component of the Total Product Life Cycle (TPLC) approach embraced by the Center for device evaluation. Under the Tissue/Material Program Area, OST scientists have undertaken mechanistic studies to better understand the role of macrophages in the phagocytosis of particles and the ability of endotoxin to potentiate of latex allergy. The expertise and data obtained from these research projects position the Center to ask the right questions for regulatory decision making. OST molecular biologists in collaboration with ORA/WEAC initiated participation 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.

Developing new approaches for medical device toxicology and risk assessment. Medical device toxicology and risk assessment pose a unique set of challenges, and OST staff are developing new, cutting-edge approaches to address these challenges. Efforts in toxicology methods development are focused on developing more sensitive, predictive tests for screening medical device materials

and to reduce the use of animals for testing purposes. OST has an extensive, productive research program to develop new molecular biomarkers of exposure and toxicity for compounds released from medical device materials. OST scientists are also adapting existing toxicology test methods to use in assessing medial device materials. For example, new approaches are being developed to assess the potential for devices that polymerize in tissue, such as bone cements, dental acrylics and tissue sealants, to produce cytotoxic effects. Furthermore, research efforts in latex glove allergies have provided the Center with an independent source of data to support regulatory decision-making. Similar to the adaptation of toxicology research methods for medical devices, the methods used to assess the risk posed by exposure to industrial or environmental compounds must be modified when assessing the risk posed by exposure to compounds released from medical devices. OST contributed extensively to the major risk assessment of the re-use of single use devices, extensive contributions through the preparation of materials, review of documents, consultations on requested concerns, development of testing strategies and presentations at the Center level, and to external CDRH regulatory authorities. In response to the challenge, OST has spearheaded a *risk assessment methods development* program. Much of the work being done in this program is specifically intended to address issues raised during the development of the ISO/DIS 10993-17 standard.

Large Animal Models of Vascular Disease and Therapeutic Device Interventions
Key words: cardiovascular disease, balloon angioplasty, restenosis

CDRH has established a large animal cardiovascular research program to develop and study models of cardiovascular disease and therapeutic device interventions. OST is establishing animal models of vascular disease in order to investigate the safety and effectiveness of therapeutic interventions such as balloon angioplasty or stents in coronary and carotid blood vessels. This work has demonstrated that angioplasty balloon-induced coronary stenosis is dependent on balloon sizing, is gender-differentiated, and is influenced by the hormonal milieu in a domestic pig. These animal models provide the basis for investigating the biologic response (e.g., restenosis) to long-term medical device implants such as balloons or stents. The research goals include improved understanding of both the mechanisms of action and the failure modes for these interventions.

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implants such as balloons or stents. The research goals include improved understanding of both the mechanisms of action and the failure modes for these interventions.

Evaluation of *In Situ* Polymers – Test Methods Development
Key words: *in situ* polymers, biocompatibility standard, bone cements, dental acrylics

Current biocompatibility standards, i.e., ASTM (F748) and ISO (TC194-10993-1), provide a framework testing medical devices that are in a final end-stage, finished form. They do not address devices that polymerize in the tissue, such as bone cements, dental acrylics, and tissue sealants. These polymers, such as dental and bone cements, are characterized by the rapid unification of two or more compounds placed directly in tissues to form a unique product. This type of reaction can generate heat, acid, free radicals, and other products with unknown modes of action, even though the final polymer may be biocompatible. To better estimate the cytotoxicity of these *in situ* polymers, various means of introducing the reacting material to cells in culture were developed. Coating the material on a sterile glass cover slip, then adding the cover slip to the *in vitro* test system immediately provided reasonable cytotoxicity data that reflected actual use conditions. For *in situ* polymeric devices that are more viscous, such as dental materials and bone cements, a mold was used which was placed directly into cell culture. As manufacturers submit new materials and applications for *in situ* polymers, the independent data and new test methods developed by OST scientists will provide CDRH with the knowledge and expertise to evaluate product safety.

Particulate Debris and Chronic Inflammatory Responses – In Vitro Methods
Key words: *in vitro* methods, macrophages, phagocytosis, particles, wear debris, titanium, cadmium oxide, immunomodulation, inflammation

OST scientists are using cultured macrophages to understand the immunotoxic and inflammatory potential of particulate materials. Particles from orthopedic implants have been shown to induce inflammatory responses in the host. Titanium alloy (TiAlV) particles were tested alone and with lipopolysaccharide (LPS) in an *in vitro* system to determine their effects on the induction of cytokines. It was found that TiAlV particles are not very inflammatory in terms of the three cytokines and nitric oxide that were measured. The *in vitro* data on various particulate debris were used for an ASTM test method to assess biocompatibility of device particles. The data are being used to determine if there is a correlation between *in vitro* and *in vivo* findings. Together, the *in vitro* and *in vivo* studies will be used to develop risk analyses for particulates from medical devices, to write guidance documents, and to improve ASTM and ISO/AAMI standards.

Because of the important role of macrophages in the phagocytosis of foreign particles related to wear debris from implants, OST scientists assessed the effects of particulate (enter cells via phagocytosis) and soluble (enter cells via diffusion or transport mechanisms) forms of the same chemical on several endpoints (cytokine production, stress protein synthesis, nitric oxide production, and cytotoxicity). This approach should

distinguish which effects, if any, may be specifically associated with the particulate or soluble forms. Cadmium chloride (soluble) and cadmium oxide (particulate) were chosen since cadmium possesses known immunomodulatory properties. The results showed that macrophages respond similarly *in vitro* to a particulate and soluble form of the same material. They were published in August 2000 in *In Vitro and Molecular Toxicology* in a paper titled "*Effects of Particulate and Soluble Cadmium Species on Biochemical and Functional Parameters in Cultured Murine Macrophages*."

Particulate Debris and Chronic Inflammatory Responses – In Vivo Methods

Key words: *in vivo* methods, immunotoxicity, PMMA, polystyrene, polyethylene, spleen, lymphocytes

The purpose of this study is to evaluate the *in vivo* effects of biomaterial particles on macrophages and possible long-term impacts on immune functions of the host. The studies in mice indicated that polystyrene (PS) and polyethylene (PE) particles injected intraperitoneally are relatively inert materials, deposited in the omentum fatty tissues and caused only a transient inflammatory reaction. However, the polymethylmethacrylate (PMMA) particle injection lead to infiltration of activated macrophages into the spleen and to a marked involvement of splenic lymphocytes. The data show that the chemistry of material is a determining factor in signaling macrophage migration and chemotactic factor production. In addition, PE appeared to be a good candidate for use as a negative reference in the evaluation of biomaterial immunotoxicity.

Improvement of Natural Rubber Latex (NRL) Protein Quantitation Accuracy

Key words: natural rubber latex, latex allergies, protein quantitation

OST was involved in developing a method for quantitation of natural rubber latex (NRL) proteins, which recently became a national standard, ASTM D6499. The research was focused on modifying the protocol to include the measurement of glove powder-bound proteins, which may contain 10-20% of total amount of the protein on the NRL product. To validate the ASTM D6499 measurements for potential sensitization, they were compared with other NRL protein methods. Depending on the source of antigen, the ASTM D6499 correlated either with total protein level or with allergen level obtained by the RAST test. The data showed that a proper selection of standard reagent is critical for the test endpoint.

Effects of Hospital Environmental Factors on NRL Allergy

Key words: latex proteins, endotoxin, glutaraldehyde, IgE antibodies

This study is designed to determine if the endotoxin and glutaraldehyde, present on the medical devices and in the hospital environment, may be contributing factors in the development of latex allergy. Studies indicated that animals exposed to endotoxin concomitant with latex proteins developed an elevated level of IgE antibodies. Exposure to endotoxin (LPS) and latex proteins resulted in both suppression and enhancement of

the IgE antibody level, depending on the dose of LPS. The data indicate that hospital environment may contain factors that may contribute to the sensitization to NRL proteins.

Medical Glove Reclassification Rule

Key words: medical gloves, natural rubber latex, proteins, reclassification, proposed rule, labeling

Experimental and clinical studies demonstrate that cornstarch on surgical gloves can enhance foreign body reactions, increase infections, and act as a carrier of natural latex allergens. OST has provided leadership in defining the issues and developing a proposed rule to address these adverse health effects. The proposed rule, published in 1999, would require (1) new label caution statements that include recommended maximum limits for protein, glove powder, and powder-free residue; (2) labeling of protein levels on NRL gloves; (3) labeling powder levels on powdered NRL and synthetic gloves; and (4) expiration labeling supported by stability studies. The comments received on the proposed rule have been analyzed, responses to the issues raised have been drafted, and options to the proposed labeling statements were tested by a focus group. Based on the analysis of comments and the results of the focus testing, the text of the final regulation has been drafted and the preamble to the rule and the medical glove guidance document are being revised. After senior staff approval, the final rule will be sent to FDA/OCC.

Molecular Biomarkers for Preclinical Evaluation of Medical Device Materials

Key words: kidney, nephrotoxicity, stress proteins, heat shock proteins, preclinical test method development

OST scientists develop predictive preclinical methods for improved safety assessments, standards, and risk assessments. New molecular biomarkers of exposure and toxicity must be carefully validated with traditional assays and standards for use in preclinical safety evaluation and in risk assessment activities. The rationale for assessing biomarkers at the cellular and molecular level are that such targets are usually the first responses induced by potentially hazardous materials and chemicals. OST scientists are evaluating the "stress" protein response, sometimes called heat shock proteins, as a method that will serve as a screening assay to more readily predict potential adverse effects of device materials and other chemicals in major target systems in the body, such as the kidney, liver, and endocrine system. To be effective and useful, a biomarker should be detectable earlier than the onset of overt tissue damage. OST scientists published a paper in February 2000 in *Toxicological Sciences* titled "*Mercury induces regional and cell-specific heat shock protein expression in rat kidney*." The data demonstrated that the expression of specific proteins in response to mercury exposure correlated with the ensuing development of kidney damage. Further evaluation of these biomarkers within specific major morphological regions and cell types within the kidney demonstrated that cells that do not or are unable to express these proteins in response to nephrotoxicant exposure might be more susceptible to damage.

Molecular Biomarkers for Endocrine Disruption by Medical Device Materials
Key words: endocrine disruption, women's health, bisphenol A, hazard analysis, mode of action

Certain plasticizers found in some medical device plastics or used in device manufacture may be potential endocrine disrupters, i.e., mimic or interfere with endogenous endocrine and hormone homeostasis. OST scientists are collaborating with researchers at the George Washington University assessing the estrogenic properties of bisphenol A (BPA), a plasticizer found in medical tubing and dental sealants. Three endpoints (uterine hypertrophy, histology, and expression of specific proteins, called heat shock proteins) were used to evaluate modifications and enhancements to the traditional assay for estrogenic effects of BPA in mice. The results have shown that expression of specific heat shock proteins is an estrogenic effect independent of uterine swelling and is a more sensitive indicator of estrogenic effect than uterine swelling. The OST modifications provide additional biomarkers of effect that expand the mechanistic information derived from the assay and will reduce the number of uncertainties in assessing risk from exposure to estrogenic materials. Results of these experiments were published in *Toxicological Sciences*, a leading toxicology journal. The paper was designated "Highlight Paper of the Month" and was titled "*Bisphenol-A induced increase in uterine weight and alterations in uterine morphology in ovariectomized mice: Role of the estrogen receptor*".

DEHP Risk Assessment
Key words: DEHP, phthalate, PVC medical devices, risk assessment

In late FY 1999, a citizen's petition was submitted to the FDA Commissioner, requesting the Agency 1) initiate a rule or issue guidance consistently requiring all PVC medical devices that may leach phthalate plasticizers include a prominent, clearly worded warning label as to the potential for DEHP or other phthalate plasticizers to leach out of the PVC and to enter the body, and 2) establish a program to expedite the development and use of substitutes for PVC medical devices that leach phthalate plasticizers. To determine if such actions are warranted, it is important to first assess the risk posed by patient exposure to DEHP. In FY 2000, OST prepared a risk assessment of DEHP released from medical devices and submitted it for review to each FDA Center. Based on the comments received, the risk assessment was revised in FY 2000. Because of the cross-cutting nature of the issues addressed in the risk assessment, the document was also submitted to the FDA Senior Science Council, where it is currently under review.

Risk Assessment of Dioxin in Tampons
Key words: dioxins, tampons, risk assessment

Over the past 2 years, OST scientists have developed a risk assessment examining the potential for harmful affects from dioxin in tampons. Congress and the press initially raised concerns because most tampons contain rayon made from cellulose fibers that might contain dioxin due to the manufacturing process of the rayon. Openly published

data of the chemical analysis of tampons indicated that little or no dioxin was present, but that there were small amounts of related compounds. OST scientists evaluated the results of the chemical analysis, usage patterns and exposures, and a new risk assessment approach was undertaken to revise this document. The hazards from tampon use were calculated, and the amount of additional exposure to dioxin from tampons was found to be infinitesimal, presenting negligible additional risk for adverse effects.

Tissue Engineering

The Molecular Biology Branch of OST served as Chair of the FDA InterCenter Tissue Engineering Working Group, providing leadership in programs to develop guidance and planning options to the Center and Agency. These encompass the following: 1) technology monitoring and assessment; 2) evaluating applications in medical products; 3) 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 to facilitate scientific and regulatory assessment of new biotechnology-derived and tissue-engineered medical products (TEMPs).

These products have focused on addressing the scientific and regulatory considerations for new products and developing information for Center/Agency decision making. 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 research and development community, and participating in the development of cooperative programs with other Federal agencies, such as the MATES Working Group of the Subcommittee on Biotechnology, under the broad umbrella of the Office of Science Technology Policy.

WIRELESS TECHNOLOGIES

The simultaneous emergence of the wireless technology revolution and a flood of devices incorporating sensitive microelectronics are leading to a highly unstable situation in which medical devices with electronics can be highly sensitive to electromagnetic interference. In FY 2000, OST investigated the potential interaction between electromagnetic security systems (e.g., electronic article surveillance systems) and implanted medical devices, such as pacemakers and neurostimulators. Further, OST helped lead a successful collaboration with the Federal Communications commission (FCC) and the American Hospital Association to establish the first Wireless Medical Telemetry Service with protections for the vital patient signals. In addition, OST responded to concerns about the radiation from cellular telephones to develop a model that predicts human absorption of radiation emitted by these products. During this year, this program contributed to (1) the development of a guidance document for medical device manufacturers and users to assess the risks of electromagnetic interference

(EMI) with wireless medical telemetry, (2) labeling recommendations for electronic anti-theft security systems, and (3) the review of warnings in the labeling for implanted cardiac and nerve stimulation devices. Additionally, the program contributed to the regulatory review of many device submissions, including implanted and external cardiac stimulation devices, ultrasonic bone densitometers, Benign Prostatic Hyperplasia hyperthermia devices, and powered wheelchairs and scooters. OST provided substantial input for the development of national consensus standards for hearing aid electromagnetic compatibility (EMC) with cellular telephones, EMC of implanted cardiac stimulation devices, and the revision of a recommended practice for ad hoc EMI testing of medical device devices with portable radio transmitters, as well as for an international consensus standard for powered wheelchair EMC. Relating to human absorption of emitted radiation, OST programs contributed to the development of standard phantoms and test methodologies. Furthermore, construction of a quality assurance facility at the University of Maryland and the OST in-house measurement facility proceeded on schedule.

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

Key words: electromagnetic compatibility, metal detectors, electronic surveillance systems, cardiac pacemaker, EMC

This project involves evaluating implantable medical devices for their susceptibility to electromagnetic interference (EMI) from electronic article surveillance systems (EASS) and other security systems. EASS are used in many retail stores to prevent shoplifting by detecting special tags placed on merchandise. 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. Because of the great similarity of EASS with magnetic-field-emitting metal detectors, this project was expanded to include evaluating EMI from metal detectors. Emissions were measured from nine different hand-held metal detectors and one walk-through metal detector this fiscal year. This project is closely associated with the OST project "Laboratory Testing of Cardiac and Electrical Stimulation Devices." This project 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).

Measurement of Electromagnetic Energy Delivered to Models of Humans by Medical Devices

Key words: cellular telephone, specific absorption rate, brain, quality assurance

This project is focused on the support of a critical emerging voluntary standard for testing the radiation safety of cellular phones and other wireless handsets. This technical standard defines detailed test methods for wireless phones and is being developed by the Institute of Electrical and Electronic Engineers (IEEE) with the strong participation and leadership of OST/CDRH. The standard, "Recommended Practice for Determining the

Spatial-Peak Specific Absorption Rate (SAR) in the Human Body Due to Wireless Communications Devices: Experimental Techniques," sets forth the first consistent test methodology for measuring the Specific Absorption Rate (SAR) produced in a tissue-simulating human head model by cellular telephones. The lack of a standardized SAR test methodology has lead to widely varying results when the same telephone is measured at different laboratories. This variability has necessitated recalls of phones by the Federal Communications Commission, who regulates these devices in the U.S. In support of the development of the IEEE test method, CDRH began developing a measurement laboratory for determining SAR precisely. Working in collaboration with the University of Maryland (UMD), OST is also developing an SAR measurement quality assurance (QA) facility. CDRH and UMD will build and circulate an SAR evaluation system to laboratories that make cellular telephone SAR measurements. These labs will include government agencies and cellular phone manufacturers throughout the world. This QA program will ensure that by using a stable, simulated cellular phone, each laboratory can determine the SAR induced in a tissue-simulating human head model with a high degree of accuracy and precision.

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

This project is intended to assess the electromagnetic compatibility (EMC) of several high-priority ambulatory and implanted electrical stimulation medical devices. During this fiscal year, OST participated actively in finalizing a voluntary standard that defines a detailed laboratory test method for the *in vitro* evaluation of electromagnetic interference (EMI) of implanted cardiac pacemakers and defibrillators from cellular telephones. The standard was developed under the sponsorship of the Association for the Advancement of Medical Instrumentation (AAMI) Pacemaker Task Group. The standard test method is based on a method developed by OST and modified with input from various other labs, including those of medical device manufacturers. OST, the Office of Device Evaluation (ODE) in CDRH, and many other groups completed a final draft of this detailed, standardized test method in FY 2000. In another effort dealing with the EMC of Electrical Stimulation Devices, OST collaborated with personnel from ODE and the Office of Surveillance and Biometrics 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.

This work was done partially in support of an Interagency Agreement (IAG) with the Federal Aviation Administration. The IAG deals with evaluating medical device EMI from emissions of airport security systems (metal detectors).

Wireless Medical Telemetry

Key words: wireless medical telemetry, EMI, FCC, AHA

Wireless medical telemetry (WMTS) systems are used to monitor patients at a distance in the intermediate care units of hospitals and in many other health care facilities. In recent years, failures of telemetry systems that were monitoring patients occurred because of electromagnetic interference (EMI) from the new digital television transmitters and other wireless broadcast services that shared the same frequencies as the WMTS. During FY 2000, FDA worked in partnership with the Federal Communications Commission (FCC), the American Hospital Association (AHA), telemetry manufacturers, and clinicians to help the FCC create new, dedicated frequency bands for Wireless Medical Telemetry Services (WMTS). The CDRH EMC group, led by OST, developed recommendations to address the issue of EMI and the changes to the radio services where wireless telemetry has traditionally operated. Letters were sent to telemetry manufacturers, users, and clinicians, encouraging manufacturers and users of telemetry devices to migrate to the new WMTS bands. WMTS provides protections against EMI and reduces the risk of interference to the medical telemetry from others in band radio sources. To assist manufacturers in bringing products using the WMTS to market in a least burdensome manner, a guidance document titled "Deciding when to Submit a New 510(k) for a Change to an Existing Wireless Medical Telemetry Device" was developed. Information about the wireless medical telemetry EMI issue, and links to the guidance, wee published on the FDA/CDRH web page.

X-RAY INSTRUMENT CALIBRATION, FIELD SUPPORT, AND 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 the routine compliance programs and all related field supplies; support for special measurements needed by field personnel such as measuring CT beam profiles; measuring radiation from contaminated medical products, etc.; 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 Calibration Laboratory

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

OST is responsible for the traceability to National Standards of ionizing radiation measurements made by FDA or used in FDA compliance programs. This mission is fulfilled by operating a secondary standard laboratory accredited by the National Voluntary Laboratory Accreditation Program (NVLAP). In FY 2000, a total of 1,750

accredited calibrations of radiation measuring instruments were performed by irradiation in known x-ray fields. Additionally, 704 electrical pre-calibrations of instruments and 149 calibrations of noninvasive kVp meters 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 2000, 65% of the calibrations were for instruments owned by FDA, 30% for instruments owned by state agencies, and 5% for instruments owned by other federal agencies. A significant 72% of the instruments calibrated were designated for testing compliance with the RCHSA of 1968. Another 21 % were designated for testing compliance with the Mammography Quality Standards Reauthorization Act of 1998. The remaining 7 % of the instrument calibrations were in support of the Nationwide Evaluation of X-ray Trends (NEXT). OST keeps track of approximately 2800 pieces of equipment, including information on instrument usage and calibration data. The instruments are located at over 500 inspector stations throughout the country and U.S. territories.

In May 2000, following a site inspection by NVLAP, the laboratory received accreditation for 13 mammography calibration beams. These x-ray beams were added to the general diagnostic beams already in the Scope of Accreditation. As required by NVLAP, the laboratory this year has participated in a Proficiency Test administered by the National Institute of Standards and Technology (NIST) and has undergone an internal audit of operating procedures and of the Quality System.

Radiation Safety 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 security screening. Several installations of x-ray security scanners are presently in operation in this country. FDA has regulatory jurisdiction over these devices. OST has led the effort to develop an ANSI Health Physics Society consensus standard to address the radiation safety issues of this practice. The group convened in November 1999 and, after one year, is close to completing a first draft of the standard. It is anticipated that the new standard will be an important influence on the way these products are regulated. OST staff have given presentations to the TEPRSSC (Technical Electronic Product Radiation Safety Standards Committee) on this effort.

Dosimetry Evaluations In Premarket Submissions

Key words: dosimetry, PTCA, restenosis, brachytherapy

Every year more than 500,000 patients are treated with percutaneous transluminal coronary angioplasty (PTCA) for heart-related problems. Of these, over 300,000 will have a stent implanted, and 30 to 40% of them will need to be treated for restenosis. Ionizing radiation has shown some promise in reducing the number of in-stent restenoses. OST has performed the dosimetry evaluation for IDE and PMA submissions using intravascular brachytherapy sources to inhibit restenosis. The dosimetry for intravascular brachytherapy differs significantly from conventional low-energy interstitial

brachytherapy in that the dose at millimeter distances from the sources is critical. In addition, there are numerous source designs, various source isotopes, and different dose rates versus distance from source distributions. These variations add more complications to evaluating the dosimetry associated with these sources in determining the safety and efficacy of the device. Similarly, OST scientists have taken an active role in standardizing the dosimetry for palladium and iodine brachytherapy seeds used in the treatment of prostate cancer. The Office has provided the FDA liaison to the American Association of Physicists in Medicine (AAPM) and to the Council of Ionizing Radiation Measurements and Standards (CIRMS) to ensure that FDA's concerns related to measuring radiation from medical equipment and brachytherapy sources are addressed. OST staff has also served on an ad hoc committee and worked with the Nuclear Regulatory Commission and ORA on calibration and production issues. A series of six lectures entitled, "Ionizing Radiation Primer" were provided to the ODE reviewers responsible for intravascular brachytherapy devices.

Technical Standards Development

Keywords: NCCLS, ANSI, standards, automation

OST serves as the government representative on the NCCLS Area Committee on Laboratory Automation. FDA comments were incorporated into the five standards developed by this committee. FDA comments noted that the elements of the standard only represent a portion of a complete life-cycle development process, and a note alerting users to that fact is included in each of the standards. FDA also provided other comments identifying the need to develop standard conformance processes for these and subsequent standards. The standards were completed within the ambitious time frame established at the beginning of the committee's deliberations.

OST represents CDRH at the quarterly meetings of the ANSI Healthcare Informatics Standards Board (HISB). HISB acts to coordinate standards development for a computerized patient record and has solicited comment from CDRH on any regulatory impact such standards might have on FDA regulatory activities. OST has arranged for HISB to hear information on the status of recognized standards, NDC code regulation, and FDA's electronic signature regulations. Scientists also provided reports on regulatory guidance on computer product regulations as well as FDA's initiatives for electronic data transmission and encryption. Based on information from OST staff, HISB was provided a high-level overview of a "requirements" document that HISB might use in developing its web site. This document emphasized the requirements for meeting the needs of a very diverse user population like that connecting to FDA's web site.

Re-Engineering FDA's Regulated Product Information System

Key words: re-engineering, prototype

OST participated in a workgroup investigating problems the Center encounters when obtaining data from its existing data systems. OST prepared a list of over 200 "needs," based on a sample user population in the Center, ORA, CDER, and CBER. This report

served as the basis of a presentation to senior staff on issues that should be addressed by developing an information system more suited to the changes in technology and information needs of an “electronic business” scenario that exists today. OST is providing technical advice on a prototype requirements document for senior staff to review as they consider the feasibility of developing an information system that can better serve the needs of staff in order to provide timely and appropriate regulatory response to public health issues.

Appendix A – OST PUBLICATIONS

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Silberberg JL. Update on the draft second edition of international standard IEC 60601-1-2 for EMC of medical electrical equipment. 2000 IEEE International Symposium on EMC, Workshops and Tutorials, abstract, Washington, DC, August 21-25, 2000.

Soykan O, Silberberg JL. The effect of excitation frequency on transthoracic impedance measurement. Digest of papers of the 2000 World Congress on Medical Physics and Biomedical Engineering and the Proceedings of the 22nd Annual International Conference of the IEEE Engineering in Medicine and Biology Society, abstract, July 23-28, 2000.

Stratmeyer ME, Brown RP. Risk assessment-based approach for the biological evaluation of medical device materials. Society of Toxicology Annual Meeting, Philadelphia, PA, March 19-23, 2000.

Tadokoro T, Kobayashi N, Beer JZ, Zmudzka BZ, Korossy KS, Hearing VJ. Analysis of UV-induced DNA damage in skin within racial/ethnic groups. *Pigment Cell Research* **13:**216, 2000.

Tadokoro T, Kobayashi N, Beer JZ, Zmudzka BZ, Korossy KS, Hearing VJ. Examination of DNA damage induced by ultraviolet irradiation of human skin within racial/ethnic groups. *Pigment Cell Research,* **13:** 399, 2000.

Tadokoro T, Kobayashi N, Beer JZ, Zmudzka BZ, Korossy KS, Hearing VJ. Analysis of UV-induced DNA damage in skin within racial/ethnic groups. The 9th Meeting of the Pan American Society for Pigment Cell Research, College Station, TX, June 25-28, 2000.

The Photosciences Network (with contributors in CDER, CDRH, CFSAN, NCTR and NCI/NIH). Quantitative, biologically relevant parameters for testing and standardization of skin response to UV. 2000 FDA Science Forum, FDA and the Science of Safety: New Perspectives, Washington, DC. p. 54, February 14-15, 2000.

Wear KA. A model for ultrasonic backscatter from trabecular bone. Proceedings of the IEEE Symposium on Ultrasonics **2**:1307-1310, 1999.

Witters DM. Planning for the future: addressing electromagnetic interference (EMI) risks with the new dedicated wireless medical telemetry service. NCHES 4th Annual Conference, Bethesda, MD, May 2, 2000.

Witters DM. Wireless medical telemetry: the FDA perspective fore the proposed wireless medical telemetry service. ACCE/AAMI 2000, San Jose, CA, June 3, 2000.

Witters DM. Medical device electromagnetic compatibility: reducing the risks of EMI in healthcare facilities in the wireless age. New England Healthcare Engineering Society Workshop, Boston, MA, November 2, 2000.

Woods TO, Brown SA, Merritt K, Hitchins VM. The effect of repeated ethylene oxide sterilization on the mechanical strength of synthetic absorbable sutures. FDA 2000 Science Forum, FDA and the Science of Safety: New Perspectives, Washington, DC, February 14-15, 2000.

Woods TO, Brown SA, Merritt K, Hitchins VM. The effect of reprocessing on single use electrophysiology catheters. FDA 2000 Science Forum, FDA and the Science of Safety: New Perspectives, Washington, DC, February 14-15, 2000.

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. 13th International Congress on Photobiology, San Francisco, July 1-6, 2000, Abstracts, p.195.

OST Internal Reports

Busick DN. Laboratory evaluation of the system 0_2 portable oxygen delivery system. DMMS Report #00-03, August 2000.

APPENDIX B - OST PRESENTATIONS

October 1, 1999 – September 30, 2000

Alqahtani J, McLean I, Weiblinger R, Ediger M. Corneal ablation with low fluence excimer laser. Presented at AAO Annual Meeting, Orlando, FL, October 24-27, 1999.

Beer JZ, Bushar HF, Chwirut DJ, Ediger MN, Lee W, Matchette LS, Miller SA, Lopez H, Weininger S, Zmudzka BZ. How to measure UV response in human skin? 2000 FDA Science Forum, FDA and the Science of Safety: New Perspectives, Washington, DC, February 14-15, 2000.

Beer JZ, Hearing VJ. UV or not UV, that is the question. National Cancer Institute, Bethesda, MD, June 20, 2000.

Brown SA. On methods used for corrosion testing of NiTi. Shape Memory and Superelastic Technologies, Pacific Grove, CA, April 2000.

Brown SA, Merritt K, Woods TO, Hitchins VM. The effects of use and simulated reuse on PTCA balloons and catheters. Transactions of the 6th World Congress of Biomaterials, Kamuela, HI, p. 462, May 19, 2000.

Bushar GS, Lyle DB, Langone JJ. Development of a standard methodology for screening medical device materials for alternative pathway complement activation. Immunology 2000, Seattle, WA, May 12-16, 2000.

Byrnes GA, Miller SA, Mazur DO, Grossman LW. Laser characteristics through fundus contact treatment lenses: risk potential for anterior segment complications, presented at Annual Meeting of Association for Research in Vision and Ophthalmology (ARVO), Ft. Lauderdale, FL, April 6 - May 4, 2000.

Chwirut DJ. General interest members perspective on Committee F4 Standards. Workshop on Past, Present, and Future, ASTM Committee F04, Toronto, Canada, May 2000.

Elespuru RE. Summary principles and case studies: CDER genetic toxicology course, Rockville, MD, June 14, 2000.

Elespuru RE. Genetic toxicology: CDRH biocompatibility course, Gaithersburg, MD, May 17, 2000.

Elespuru RE. In vitro p53 mutagenicity assay for use in cancer risk assessment. FDA Science Forum poster presentation, Washington, DC, February 14, 2000.

Elespuru RE. The background and principles of genetic toxicology testing. CDER Genetic Toxicology Course, April 26, 2000.

Ediger MN. Emerging technologies in biomedical optics. Presented at National Research Council, Washington, DC, January 4, 2000.

Ediger MN. Optical diagnostic medical devices - considerations for clinical trials and market clearance in the US. Presented at Shedding New Light on Disease: Optical Diagnostics for the Millennium, NRC Canada, Winnipeg, Canada, June 26, 2000.

Godar DE. Full-spectrum apoptosis: vive la difference. International Congress of Photobiology (ICP), San Francisco, CA, July 2000.

Godar DE. UVA1 radiation triggers two different final apoptotic pathways. 13th International Congress on Photobiology, San Francison, CA, July 1-6, 2000.

Heaton HT, Phillips RA. FDA and brachytherapy sources. AAPM North Central Chapter, Madison, WI, October 7, 1999.

Heaton HT. MPDs for the NEEDs 3 report - possible new programs. Eighth Annual Meeting of the Council of Ionizing Radiation Measurements and Standard, National Institute of Standards and Technology, Gaithersburg, MD, October 13-15, 1999.

Heaton HT. Overview of the medical subcommittee activities. Eighth Annual Meeting of the Council of Ionizing Radiation Measurements and Standard, National Institute of Standards and Technology, Gaithersburg, MD, October 13-15, 1999.

Heaton HT. FDA X-ray calibration laboratory: traceability to national standards. 33d HPS Mid-Year Symposium, Virginia Beach, VA, January 30 - February 2, 2000.

Heaton HT. IDE and PMA dosimetry issues, Cardiovascular Radiation Therapy IV, Washington, DC, Feb 16-18, 2000.

Hellman KB. FDA Perspectives: biologics and devices. Update of FDA TSE Working Group Initiatives, Cambridge Healthtech Institute Conference on Transmissible Spongiform Encephalopathies, October 1999 (abstract).

Hellman KB. FDA perspectives: biologics and devices – update of FDA TSE working group initiatives, Cambridge Healthtech Institute (CHI) Conference on Transmissible Spongiform Encephalopathies (TSEs), Washington, DC, October 27-28, 1999.

Hellman KB. U.S. FDA Regulatory Initiatives for Tissue Engineered Medical Products. AIST-MITI – University of Tokyo Joint Workshop on Industrialization of Tissue Engineering, Tokyo, Japan, March 21, 2000.

Hellman KB. Tissue engineering: the regulatory perspective. Pittsburgh Orthopedic Tissue Engineering Symposium, Pittsburgh, PA, April 16-19, 2000.

Hellman KB. Review of tissue engineering in the United States. MATES and U.S. Government Tissue Engineering Initiative, WTEC Workshop, Bethesda, MD, June 5-6, 2000.

Hellman KB. Introduction to MATES and survey of FDA tissue engineering initiatives. FDA MATES Working Group Meeting, Tissue Engineering, Gaithersburg, MD, June 15, 2000.

Hellman KB. Overview and future perspectives, DARPA Focus 2000, Science/Technology at FDA, Chantilly, VA, June 29-30, 2000.

Hellman KB. Reference data on properties of biomaterials. Tissue Engineering Biomaterials, National Institute of Standards and Technology Workshop, Gaithersburg, MD, July 29, 2000.

Hellman KB. Regulatory issues for tissue engineering. Functional Tissue Engineering Workshop, Tampa, Fl, September 14-19, 2000.

Howard PC, Sams II RL, Miller BJ, Allaben WT, Okerberg C, Bucci TJ, Wamer WG, Beer JZ. Response of SKH-1 mouse skin simulated solar and UV radiation. 2000 FDA Science Forum, FDA and the Science of Safety: New Perspectives, Washington, DC, February 14-15, 2000.

Ilev IK, Waynant RW. Fiber optic based confocal microscope with submicron resolution. Presented at Optical Imaging Workshop, National Institutes of Health, Bethesda, MD, Sep 7, 2000.

Ilev IK, Waynant RW. Ultraviolet visible and infrared laser delivery using laser-to-fiber coupling via a grazing incidence-based hollow taper. Presented at European Symposium on BIOS: Europe (EUROPTO, EBIOS-2000), Amsterdam, July 4-8, 2000.

Ilev IK, Waynant RW. Submicron reflection confocal microscope with multimode fiber output. Presented at Conference of Lasers and Electro Optics (CLEO), San Francisco, CA, May 7-14, 2000.

Beer JZ, Bushar HF, Busick D, Chwirut DJ, Cyr WH, Ediger MN, Lao NT, Matchette LS, Miller SA, Lopez H, Weininger S, Zmudzka BZ. Studies on parameters of UV response in human skin: a progress report. 13th International Congress on Photobiology, San Francisco, July 1-6, 2000.

Lightfoote MM, Bushar GS, Langone JJ. Immunological responses to silicone breast implants. Innate Immunity Workshop, Aegean Conferences, Santorini, Greece, October 11-15, 2000.

Lightfoote MM, Bushar GS, Langone JJ. Immunological responses to silicone breast implants. Lymphocyte Signaling, Aegean Conferences, October 16-20, 2000, Santorini, Greece.

Luu HMD, Hutter JC. Poster presentation: A physiologically based pharmacokinetic modeling of octamethylcyclostetrasiloxane (D4). American Chemical Society, San Francisco, CA, April 2000.

Lyle DB, Bushar GS, Langone JJ. Development of a standard methodology for screening medical device materials for alternative pathway complement activation. Proceedings, FDA Science Forum, Washington, DC, February 14-15, 2000.

Miller SA, Zmudzka BZ, Matchette LS, Beer JZ. Ultraviolet radiation exposure from diagnostic medical devices – preliminary evaluation of acute risks. Presented at International Workshop on UV Radiation Exposure, Measurement, and Protection, Oxford, UK, Oct 18-20, 1999.

Owen RD. Biological effects and health consequences of RF fields. 4th International Non-Ionizing Radiation Workshop, International Commission on Non-Ionizing Radiation Protection, Kyoto, Japan, June 24, 2000.

Owen RD. The biological effects of ELF-EMF and the results of US research. Symposium on Electromagnetic Fields and Health, Agency of National Resources and Energy (ANRE) of the Japanese Ministry of International Trade and Industries (MITI) and Japan Electrical Safety & Environment Technology Laboratories, Tokyo, Japan, June 19 2000.

Royston DD. Laser sources in TMLR and PMR: effects and performance measurements. Presented at Workshop on Cardiovascular Applications of Lasers, FDA, Center for Veterinary Medicine, Laurel, MD, May 9-10, 2000.

Schroeder LW. Packaging medical products made of natural rubber latex. Conference on Medical Packaging, Center for Business Intelligence, Washington, DC, December 10-11, 1999.

Shope TB. Perspectives on radiation injuries from fluoroscopy. World Congress on Medical Physics and Biomedical Engineering (Introduction to Refresher Course on "Injuries from Fluoroscopy, What They Are, Why They Occur and How to Avoid Them"), Chicago, IL, July 27, 2000.

Silberberg JL, Boyd SM, Heirman DN. On-site medical device immunity testing (seminar and workshop on ANSI C63.18), sponsored by the US EMC Standards Corporation and the University of Oklahoma Center for the Study of Wireless EMC, Walter Reed Army Medical Center, Washington, DC, November 8-9, 1999.

Silberberg JL. Update on the draft second edition of international standard IEC 60601-1-2 for EMC of medical electrical equipment. 2000 IEEE International Symposium on EMC, Washington, DC, August 21-25, 2000.

Tadokoro T, Kobayashi N, Beer JZ, Zmudzka BZ, Korossy KS, Hearing VJ. Examination of DNA damage induced by ultraviolet irradiation of human skin within racial/ethnic groups. 9th Meeting of the European Society for Pigment Cell Research, Ulm, Germany, September 27-October 1, 2000.

The Photosciences Network (with contributors in CDER, CDRH, CFSAN, NCTR and NCI/NIH). Quantitative, biologically relevant parameters for testing and standardization of skin response to UV. 2000 FDA Science Forum, FDA and the Science of Safety: New Perspectives, Washington, DC, February 14-15, 2000.

Wear KA. A model for ultrasonic backscatter from trabecular bone. 1999 IEEE Ultrasonics Symposium, Lake Tahoe, CA, October 17-21, 1999.

Wear KA. Comparison of phase and group velocities in trabecular bone, Proceedings of the 25th International Symposium on Ultrasonic Imaging and Tissue Characterization, Arlington, VA, May 22-24, 2000.

Wear KA. Variations in transit-time-based ultrasonic velocity estimates in human calcaneus due to frequency-dependent attenuation and dispersion, Proceedings of the SPIE Medical Imaging 2000 Conference, San Diego, CA, February 12-17, 2000.

Wear KA. Fundamental mechanisms underlying broadband ultrasonic attenuation and backscattering in calcaneus. American Society of Bone and Mineral Research 22nd Annual Meeting, Toronto, Ontario, Canada, September 22 - 26, 2000. Received award for fifth place poster (out of 37) in ultrasound category.

Wear KA. Sources of disparity for transit-time-based and frequency-domain-based sound speed measurements in trabecular bone. Amer. Soc. Bone Min. Res. 22nd Annual Meeting, Toronto, Ontario, Canada, September 22 - 26, 2000.

Witters DM. Planning for the future: addressing electromagnetic interference (EMI) risks with the new dedicated wireless medical telemetry service. NCHES 4th Annual Conference "Ending the Millennium," National Capital Healthcare Engineering Society (NCHES), Bethesda, MD, May 2, 2000.

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. 13th International Congress on Photobiology, San Francisco, July 1-6, 2000.

APPENDIX C - Academic Affiliations of OST Staff

October 1, 1999 - September 30, 2000

Chenault, V. Michelle, Ph.D.	Uniformed Services University of the Health Sciences Adjunct Assistant Professor
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
Grossman, Laurence W., Ph.D.	Georgetown University Medical Center Department of Radiology Adjunct Associate Professor
Hilbert, Stephen L., M.D., Ph.D.	Brown University School of Medicine Department of Surgery Division of Cardiothoracic Surgery Adjunct Professor of Surgery
Krauthamer, Victor, Ph.D.	Uniformed Services University for Health Services Department of Anatomy and Physiology 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 Lecturer/Instructor
Myers, Kyle J., Ph.D.	Georgetown University Medical Center Department of Radiology Adjunct Associate Professor University of Arizona Optical Sciences Center Adjunct Professor
Picciolo, Grace L.	Clemson University Department of Bioengineering Adjunct Professor
Umbreit, Thomas H.	University of Medicine and Dentistry of New Jersey Robert Wood Johnson Medical School Environmental and Occupational Health Sciences Institute Department of Environmental and Community Medicine Adjunct Assistant Professor
Waynant, Ronald W., Ph.D.	Catholic University of America Electrical Engineering Department Adjunct Associate Professor Uniformed Services University of the Health Sciences Radiology Department
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, 1999 – September 30, 2000

Patents Pending

Matchette LS, Beer JZ, Ediger MN, Miller SA, Durkin A, Lenderink E. Spatially Resolved Diffuse Reflectance in Determining Skin UV Sensitivity. Submitted to DPS 8/4/00.

APPENDIX E - OST- Sponsored Seminars

October 1, 1999 – September 30, 2000

Luu HMD. Sample Preparation, Biocompatibility Course, Staff College, Food and Drug Administration, Center for Devices and Radiological Health, Rockville, MD, Spring 2000.

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

October 1, 1999 – September 30, 2000

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

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) (43-00). 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 Institute of Environmental Heath Sciences (NIEHS) (FDA-223-94-6015). Support to the Center for Devices and Radiological Health on the effects of ionizing and non-ionizing radiation.

National Institute of Health (NIH) (FDA-224-00-6068). Models of thermal ablation computational, in-vitro, in-vivo.

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

Office of Naval Research (ONR) (FDA-224-92-6007). Waveguide and fiber optic delivery for medical applications for free electron lasers.

Program for Appropriate Technology in Health (PATH) (39-99). Effects of storage, materials and stress on glove integrity.

Safeskin Corporation (32-98). Increase in prevalence of latex protein allergy.

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