Office of Science And Technology

Annual Report

Fiscal Year 1998

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.

The Office of Science and Technology (OST) supports the scientific basis for the Agency's regulatory policies through development of independent laboratory information for regulatory and other public health activities of the Center for Devices and Radiological Health (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. It provides expertise and analyses for health-risk assessments. The Office also develops new or improved measurement methods, techniques, instruments, and analytical procedures for evaluating product performance and reliability. OST provides innovative solutions to public health problems through the development of generic techniques to enhance product safety and effectiveness. 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 inform you, our constituents, of 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 1998. The Annual Report is an overview rather than a comprehensive accounting. 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. Comments are welcome 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, 1997 – September 30, 1998

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INTRODUCTION

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 decision making through development of independent laboratory information for regulatory and other public health activities of the Center for Devices and Radiological Health (CDRH). OST accomplishes this mission by working in four areas: managing, developing, and supporting standards used for regulatory assessments; providing technical consultations and performing laboratory evaluations and analyses in support of CDRH premarket and postmarket activities; developing forensic 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. In this section of the OST Annual Report these activities will be summarized and a few highlighted.

STANDARDS

The participation by CDRH in the development of consensus test methods and performance standards for medical devices and radiological products encourages participation by other sectors of the medical community and enables the Center to impact the final outcomes, insuring that Agency needs are met by these documents. This activity is focused in the Office of Science and Technology. Our standards program includes managing the program for the Center; serving as liaison to the committees of the several Standards Development Organizations that are relevant to this sector; laboratory development of information in support of test method development; and, partnering with the industry and academia in the execution of interlaboratory studies of test methods to establish their precision and bias. The Standards Program Coordination Staff, OST (SPCS), accredits the Center's liaison members of standards committees. SPCS coordinates the activities of the Center's Specialty Task Groups (STGs) and manages the development of the Center's consensus position of individual documents balloted by the various Standards Development Organizations (SDOs). **Table 1** illustrates the level of effort dedicated to the standards program in 1998 in comparison with previous years. In addition, OST staff contributes directly to the development of standards by volunteering to develop the first draft of many standards considered by the Office and Center. **Table 2** is an illustrative list of these documents developed this year. **Table 3** is a listing of the Interlaboratory Studies in which OST participated, and **Table 4** shows the new test methods developed. Finally, OST staff is actively engaged in the overall management of the standards program of the various SDO committees that are important in the development of medical device standards. **Table 5** shows the contribution of OST in committee management in 1998.

Table 1 – Consensus Standards – Level of Effort Comparison

	1996	1997	1998
Liaison Reps – CDRH	224	225	230
- OST	60	59	63
Standards efforts – CDRH	487	492	509
- OST			214
Standards trips – CDRH	98	115	109

Table 2 - Consensus Standards - Significant Contribution as an Author of New or Revised Guidance

Ethylene Oxide Residuals - AAMI
Hemolysis Testing of Materials – ASTM F756
Endoilluminator – ISO
Measurement of Optical Radiation – ISO
Safety of Electromedical Equipment – IEC 60601-1
Pulse Oximeter – ASTM F1415, ISO 9919
Abrasion of Coatings – ASTM F04
Biodegradation of Ceramics – ISO 10993-14
Guidance on the Selection of Reference Materials – ISO 10993-8
Retrieval and Analysis of Implanted Medical Devices – ASTM F571
Fretting Corrosion Testing of Modular Implant Interfaces ASTM F1875
Practice for Characterization of Particles – ASTM F1877
Method for Conducting Cyclic Polarization Potentiodynamic Polarization Measurement of Corrosion Susceptibility of Implantable Medical Devices
In-vitro Performance of Balloon-expandable Stents
ISO/IEC 15026 Information Technology – System and Software Integrity Levels
Software Engineering – ISO/IEC SC7
Acquisition and Use of Physiological Waveform Databases for Testing of Medical Devices – AAMI TIR
Software Engineering Standards – IEEE Software Standards Committee
Programmable Medical Devices – IEC 60601-1-4
Software Engineering Standard for Medical Device Software – AAMI
Guidance on EMC of Medical Devices for Clinical/Biomedical Engineers – AAMI
Recommended Practice for an On-Site, Ad Hoc Test Method for Estimating Radiated Electromagnetic Immunity of Medical Devices to Specific RF Transmitters – ANSI
EMC of Medical Electrical Equipment – Second draft second edition of IEC 60601-1-2 (IEC 62A/247/CD)
Disposable ECG Electrodes – ANSI/AAMI EC-12
IEC SC62B WG25 Computed Tomography
IEC SC62B WG24 Interventional Radiology
Application of Risk Management to Medical Devices – ISO/IEC 14971

Table 3 - Consensus Standards - Interlaboratory Studies for Determination of Precision and Bias

Ethylene Oxide Residuals - AAMI
Glove Powder – ASTM
Chemical Accelerator Residual on Gloves – ASTM
Latex Soluble Proteins - ASTM
Evaluation of Hemolytic Properties of Materials – ASTM F756

Table 4 - Consensus Standards - New Test Method Development

Glove Powder – ASTM
Chemical Accelerator Residual on Gloves – ASTM
Test Methods for in-vitro Blood Glucose Monitoring Systems
Simulator for the Performance Assessment of Pulse Oximeters – Joint EU and US Effort

Table 5 - Consensus Standards - Committee/Subcommittee/Working Group Leadership Positions

AAMI
- International Standards Committee – Don Marlowe
- ECG Electrodes – Dave Daly
- Software Committee– John Murray
- Waveform Testing Committee – Sandy Weininger
- Apnea Monitoring Committee – Jeff Silberberg
- EMC Committee – Jeff Silberberg

AIUM
- Technical Standards Committee – Hector Lopez
- Digital Measurement Subcommittee – Hector Lopez
- Scanner Performance and Evaluation Working Group – Keith Wear

AIUM/NEMA
- Joint Output Standards Subcommittee – Gerald Harris

ANSI
- Executive Standards Council Audit Subcommittee – Mel Altman
- EMC – Patient Connected Devices WG – Howard Bassen
- Accreditation Committee – John Murray

ASTM
- Board of Directors – Don Marlowe
- Committee on Technical Committee Operations – Dan Chwirut
- E48 – Biotechnology – Larry Bockstahler
- F04 – Medical and Surgical Devices and Materials

General Interest Vice Chairman – Dan Chwirut
- F04.12 – Metallic materials
  - F04.12.05 – Nitinol – Dan Chwirut
- F04.13 – Ceramic Materials – Gary Fischman
  - F04.13.04 – Polycrystalline Alumina – Gary Fischman
  - F04.13.71 – Magnesia Stabilized Zirconia – Gary Fischman
  - F04.13.18 – Beta TCP – Gary Fischman

F04.15 Subcommittee on Test Methods – Dan Chwirut
F04.15.08 – Coating Abrasion – Gary Fischman
F04.15.11 – MRI Compatibility –
Terry Woods, Chair
Marlene Skopec, secretary
F04.16 Biocompatibility Testing – Kathy Merritt
F04.16.09 – Characterization of particles –
Stan Brown
F04.18 – Device Retrieval & Analysis – Stan Brown
F04.19 – Corrosion – Stan Brown
F04.19.01 – Corrosion Fatigue Testing –
Stan Brown
F04.19.02 – Corrosion of Modular Interfaces –
Stan Brown
F04.19.03 – Method for Conducting Cyclic
Polarization Potentio-Dynamic Polarization
Measurements for Corrosion Susceptibility –
Stan Brown
F04.21 – Osteosynthesis – Don Marlowe
F04.21.01 – Bone Screw Performance
Standard – Don Marlowe
F04.30 – Cardiovascular Devices
F04.30.05 – Interventional Devices – Dan Chwirut
F04.33 – Surgical Instruments
F04.33.01 – Puncture Resistance of Sharps
Containers – Pat Dubill
F04.40 – Tissue Engineered Medical Products –
Kiki Hellman, Grace Picciolo
F04.93 – Orthotics and Prosthetics – Don Marlowe
F29.03.10 Pulse Oximeters – Sandy Weininger
IEEE
SCC28 –SC1 – Radiofrequency Radiation Hazards,
Measurement & Computations techniques –
Howard Bassen
SSC34 – Certification of Radiofrequency Safety –
Wireless Handsets - Howard Bassen
SESC – Software Engineering Standards Committee – John Murray
IEC
62C – High Energy Equipment & Nuclear Medicine Equipment
- Tom Heaton
62 WG2 Programmable Medical Electronics – Paul Jones
62 WG18 Over-temperature – Ray Walchle
65 - Functional Safety – Paul Jones
ISO/IEC
Joint Working Group on Risk Management – Harvey Rudolph, Chair, US TAG
Joint Technical Committee 1 (JTC1) – Information Technology – John Murray
JTC1 Subcommittee 7 – Software Engineering – John Murray
ISO
ISO TC 168 – Orthotics and Prosthetics – Leader, US Delegation, Don Marlowe
ISO TC 194 - Biological Evaluation of Medical Devices – Leader, US Delegation
Don Marlowe
WG 2 – Degradation - Ed Mueller
TG – Biodegradation of Ceramics – Gary Fischman
WG 12 – Sample Preparation and Reference Materials –
Don Marlowe
WG 14 – Material Characterization – Joseph Hutter
WHO International EMF Project International Advisory Committee – Russell Owens

F04. Medical and Surgical Devices

Key words: tissue responses, blood biocompatibility

OST has major input into the biocompatibility testing issues for materials to be used in surgical devices. The Office is active in proposing, writing, and evaluating these standards. During FY 98 four standards were approved and published. They were 1) Biological Responses to Particles *in vitro*; 2) Biological Responses to Particles *in vivo*; 3) Immunotoxicity; and 4) Evaluation of the Immune Response. Two standards were drafted, have passed subcommittee, and are to be balloted at main committee. These are evaluations of the local tissue response to absorbable/resorbables, and complement activation by materials that will come in contact with blood. Four existing standards were balloted for renewal with major input from OST. OST scientists have performed round robin testing on hemolytic properties of materials to make the existing ASTM standard more sensitive and reliable.

Sterilization Standards

Key words: sterilization, reuse, package integrity

OST has participated in various AAMI working groups on such sterilization issues as chemical sterilants, steam sterilization, ethylene oxide sterilizers, and ethylene oxide sterilization residues. Major input has been provided to draft standards or technical reports in these areas.

A new working group to re-evaluate sterility assurance levels (SALs) has been convened. OST is contributing to the writing of the draft standard. Research completed at OST and to be published in 1999 forms one of the scientific bases for re-evaluation.

AAMI has held several conferences and created working groups to address the concerns of reusing both single-use and reusable medical devices. OST has participated in these conferences, contributed posters, and chaired sessions. This is an ongoing matter in which OST scientists will continue to participate.

AAMI also has working groups evaluating test methods for package integrity, with OST contributing to evaluation of those methods that might be suitable. Some testing has been done of methods currently in use.

Biocompatibility

The predominant activity is related to ISO TC194 on biocompatibility of medical and surgical devices. AAMI presents the US position to ISO. Meetings are then held with AAMI and the documents are voted on, or the results of the US voting position taken to ISO.

OST has had major responsibility for revising and balloting ISO TC194-10993-10 (Irritation and Sensitization), has contributed to revision of 10993-3 (Mutagenicity and Genotoxicity Testing), and to revision of 10993-5 (Cytotoxicity and Cell Culture).

OST participated in the round robin testing of a possible positive control material for testing for cytotoxicity in cell culture. The Japanese provided the polyurethane materials.

The materials behaved as anticipated: material A was highly cytotoxic, material B was slightly cytotoxic, and material C was a noncytotoxic negative control.

OST has played a major role in developing the ISO standards on sample preparation and aspects of degradation. This includes contribution to 10993-Part 9 on identification and quantification of potential degradation products, Part 13 on identification and quantification of degradation products from polymeric medical devices, Part 15 on identification and quantification of degradation products from metals and alloys, and part 18 on chemical characterization of materials.

OST staff have also played a major role in the development of ISO/DIS 10993-17 (Method for the Establishment of Allowable Limits for Residues and Leachable Substances in Medical Devices Using Health Based Risk Assessment) The draft standard underwent significant revision at the May 1998 meeting in Washington, DC. The ISO/DIS 10993-17 standard is being developed in WG 11 of ISO TC 194. In addition, this working group is beginning the process of revising the 10093-7 standard that defines allowable limits for ethylene oxide sterilization residues. In addition to this ISO working group, OST is active in all of the standards agencies addressing the issue, including AAMI committees under AAMI jurisdiction.

An OST scientist serves as chair of a task force (TF2) convened under ISO TC194/WG 15 to develop guidelines for the development of biological evaluation standards and to more accurately define the process of conducting a biological evaluation. The inaugural meeting of the task force was held in December 1998 in Brussels, and assignments were made for the deliverables due to WG15. In addition to participating in TF2 of WG 15, OST is active in the full WG 15 as well.

All of these standards activities also impact on other standards developing groups or groups using standards. There have been interactions with these groups including, but not limited to, NIEHS, CDC, OSHA, ICCVAM, and USP. OST maintains a vigorous activity and important presence in these areas.

Medical Device Software Standard

Key words: software engineering, life cycle, design, development, medical device.

The Medical Device Software Standard is designed to provide CDRH and the Medical Device Community with a standard method for the lifecycle management of medical device software. This standard provides the foundation processes, activities, and tasks for the software engineering of medical device software. OST engineers are working with software practitioners through the Software Committee of the Association for the Advancement of Medical Instrumentation (AAMI). An OST engineer is Co-Chair of the AAMI Software Committee and is leading the effort to create this software engineering standard.

Work on this AAMI standard began in March 1998. A committee draft for comment is expected in January 1999. This standard is designed to reduce the time required for regulatory review of medical device software, first in the United States and then in all major markets worldwide. This standard identifies the minimum activities and tasks that must be accomplished to provide a regulatory agency confidence that the software has been

developed in a manner likely to produce highly reliable and safe software products. In addition, this standard provides a common framework and language that can be used by regulators, manufacturers, and their suppliers. This is the first standard specifically created as a medical device software standard. Due to its foundation nature, this standard will serve as the basis for future software standards development and recognition.

Tissue Engineering

Key words: program development, guidance/standards, technology monitoring/support, education

Biotechnology is responsible for the continued expansion of new medical products such as biohybrid devices and engineered tissues, diagnostics/detection methods for genetic and other diseases, and drug and vaccine delivery systems. The Center's biotechnology coordination project, through the CDRH Biotechnology Working Group and the FDA InterCenter Tissue Engineering Working Group (TEWG), supports regulatory activities and program development to ensure appropriate Center assessment of biotechnology products and formulation of appropriate regulatory oversight.

The Center Coordinator for Biotechnology and Chair of the TEWG has provided leadership in establishing programs to provide the Center and Agency with program guidance and planning options which encompass 1) technology monitoring and assessment; 2) options development for evaluating applications in medical products; 3) standards development for tissue engineered medical products (TEMPs); 4) educational programs for Agency research/review staff and the scientific community at large; and 5) science and regulatory policy recommendations. Several products continue to provide a strong knowledge base for the Center/Agency and facilitate scientific and regulatory review and evaluation of new biotechnology-derived and tissue-engineered medical products. These products include 1) the Spring 1998 Tissue Engineering Course, part of the FDA Staff College Course Series on Tissue Engineering; 2) development of draft standards for general issue areas and components of TEMPs through ASTM Division IV on TEMPs of Committee F04 (Chair of TEWG serves as Executive Secretary and primary FDA liaison for Division IV); 3) maintenance of the FDA InterCenter Biomaterials Compendium, a database inventory of TEMPs; 4) organization and participation in several national and international biotechnology and tissue engineering forums such as ASTM biannual meetings, Rice Institute Tissue Engineering Course, Pittsburgh Tissue Engineering Initiative (PTEI) Seminar Series, Tissue Engineering Society Annual Meeting; and 5) publications on tissue engineering science and regulatory issues, such as a book chapter in Frontiers in Tissue Engineering.

These products have focused on identifying scientific issues and developing information for Center/Agency decision making, analyzing products in review and under development, communicating information to the Agency and the scientific community through different mechanisms, educating Agency staff and the research and development community, and developing cooperative programs with other Federal agencies, industry, and academic consortia.

Tissue-Engineered Medical Products

Key words: tissue-engineered, standards

Activities for focusing the FDA on the emergent technologies for tissue repair and replacement have included educational and standards development through collaboration with other members of the FDA InterCenter Tissue Engineering Working Group.

The third in a series of courses featured invited national and international experts discussing isolation, growth and standardization of cells; design and standardization of materials; and application to tissue-engineered systems. The course was co-sponsored by three centers: CDRH, CBER, and CDER and administered by Staff College. Featured were important aspects of cells, biomaterials, and applications: skin cells, neuronal cells, stem cells, and liver cells along with their interactions with biomaterials and the mechanical and biochemical determinants of tissue design.

Standards for tissue-engineered medical products are under development through the auspices of the American Society for Testing and Materials (ASTM). A new Division IV Tissue Engineered Medical Products of ASTM Committee F-04 Medical and Surgical Materials and Devices has developed a structure containing 10 subcommittees and 20 task groups to address development of these standards. Presentations at various meetings describing the activity have resulted in recruitment of 180 members of the new Division IV from all constituencies: academia, government and industry. Draft documents are on the ASTM On-Line Forums for input by the task groups and information is available at three web sites: http://www.fda.gov/CDRH/Tisseng/TEMPS.html, http://www.pittsburgh-tissue.net/brochure/outreach/standards.html, and http://www.astm.org . A document describing an approach to a standard for products containing living cells was published by industry authors and will be made available to develop into a consensus standard through the ASTM process.

IEEE Cooperative Research And Development Agreement (CRADA)
Key words: software, standards

OST is working with The Institute of Electrical and Electronics Engineers (IEEE) to leverage resources in order to improve the quality of software in medical devices through efforts in standards development, identification of software engineering best practices, conformance assessment guidelines, education, and training.

An important step in achieving these goals is reflected in a Cooperative Research and Development Agreement (CRADA) between FDA/CDRH and the IEEE Computer Society (CS). FDA/CDRH will facilitate communication between the medical device industry and the IEEE CS for the purpose of introducing risk management concepts, useful to the medical device industry, into IEEE CS Software Engineering (SE) standards. The IEEE CS SE standards are important to software engineering practice in that they provide documentation and process details missing in international consensus standards. In addition to changes in the IEEE CS SE standards, the agreement calls for the development of SE training courses to be developed by IEEE CS which will be commercially available to the medical device industry as well as other industry sectors. Consonant with SE training courses will be the development of IEEE CS SE certification criteria to provide a measurement of SE competency.

TECHNICAL CONSULTATIONS

The organization of OST is structured along the lines of expertise, in contrast to the organization of the Offices of Device Evaluation (ODE) and Compliance (OC), which are organized along the lines of business. This enables the other Offices of the Center to identify and use specific expertise solving problems or consulting on the various regulatory functions of the Agency. These "bread-and-butter" activities of the Office also serve OST staff by placing them in everyday contact with the evolution of the industry and the use-problems that occur with devices. **Table 6** shows the relative changes in these interactions in the premarket review area over recent years. One of the areas in which OST can contribute most effectively to the Center's regulatory programs is through contribution to the development of guidance documents, such as guidance to reviewers and manufacturers related to the approval requirements of a specific product. **Table 7** is an illustrative list of these types of consultations for 1998. On occasion, the OST contribution is limited to developing and validating an appropriate test method for the determination of a specific piece of information needed for a particular device. **Table 8** is a list of these types of efforts in OST this year. OST receives many requests to provide expertise and information which cannot be characterized into any of the above tables. **Table 9** is a summary of thee requests from the Center, and **Table 10** is a summary of requests from non-CDRH sources. Finally, OST contributes to the Center's active postmarket surveillance activities. **Table 11** is a summary of those activities performed in 1998.

Table 6 – Premarket Review – Technical Consultations

	1996	1997	1998
IDE & Supplements	64	106	182
PrePMA, PMA & Supplements	42	88	156
510(k)	65	125	146

Table 7 – Premarket Review – Significant Contribution as an Author of New or Revised Guidance

Blood Oxygenator
Intraocular lens (IOL) Product Development Protocol (PDP) Guidance
Ophthalmoscope
Stentless Heart Valve
Replacement Heart Valve
Noninvasive Blood Pressure Monitor
Magnetic Resonance Imaging (MRI) Compatibility
Optical Diagnostic Devices
Extracorporeal Shock-wave Lithotripsy
In-vivo Devices for the Detection of Cervical Cancer and its Precursors
Magnetic Resonance (MR)
Picture Archive and Communication System (PACS)
Pulse Oximeters
Fetal Oximeters
Dosimetry and Measurement Issues for IDEs for Studying the Use of Radiation to Prevent Restenosis Following Angioplasty
Immunotoxicity Testing
Testing for Skin Sensitization to Chemicals in Latex Products
Ultrasound Probe Covers
Shelf Life Testing of Absorbable Devices
Accelerated Aging Protocol for Tentative Shelf Life Testing of Medical Gloves
Protocol for Real-time Aging of Medical Gloves
BSE Guidance
Replacement Rechargeable Batteries
Implantable Cardioverter Defibrillators
Needle Destruction Devices
Software Engineering
Guidance for Industry Principles of Software Validation
Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices
Guidance for Off the Shelf Software Use in Medical Devices
Guidance for Industry Computerized Systems Used in Clinical Trials
Systems Engineering
Guidance for the Development of a Product Development Protocol

Table 8 – Premarket Review – Guidance Test Method Development or Evaluation

Apnea Monitor
Blood Oxygenator
Intra-ocular Lenses
Measurement of Latex Protein on Medical Devices
Shelf Life Testing of Medical Gloves

Table 9 – Premarket Review – Miscellaneous Contributions

Guidance for Declaration of Conformity to Consensus Standards
DGRD Review Process Reinvention
Technical Electronic Product Radiation Safety Standards Committee (TEPRSSC)
Amendments to the Diagnostic X-ray Performance Standard
Dosimetry of a personal screening system for presentation
Y2K Activities
Center Working Group
Agency Working Group
Congressional Testimony
Working Group on Regulation of Talc
Working Group on Regulation of Glove Powder
Working Group on Apnea Monitor Standard
Expiration Dating Working Group
NIH/DOE RAPID ELF/EMF Exposure Facility
CDRH Reengineering Teams
PMA
Radiological Health
PDP
Standards
Biomaterials Group
Biomaterials Compendium
Needle destruct devices
Use of ROC Analysis in Clinical Trials
Applied Engineering in Support of Regulatory Decision Making
Book of Hazards
IEEE Computer Society Cooperative Research and Development Agreement
Cleanroom Software Engineering – MOU Walter Reed and FDA

Table 10 – Technical Consultations for Non-CDRH Clients

Sunscreen Monograph – Review of FR Notice – CDER
Characterization of Solar Simulator for Photocarcinogenesis Testing – CDER
Spectral measurement of solar simulator – CDER
Source Characterization of solar simulator – CDER
Evaluation of spectral measurement system – NCTR
Review of Technology Transfer Program Grants – NIST
Automated Blood Determination 510(k) – CBER
ROC Analysis Course – CBER
Diagnostic Imaging Group Study Section – NIH
International Advisory Committee for the WHO EMF Project
Reviewers of ATP Program Applications – Tissue Engineering – NIST
-- neural network implementations
San Diego County, Dept on Environmental Health – Regulations on body piercing jewelry
Ozone Generating Device (CPSC & EPA)
Breast Disease Diagnosis Coordinating Group – FDA and NCI
Clinical Trial of Optimized Mammography System – Clinical Center, NIH
OST/CDC ACTIVITIES
Cellulose Acetate Hemodialyzers
General Issues
Animal Testing
Publication "Partners"
Hemasure Filters
General Issues
Animal Testing
Publication "Partners"
Review Consultant for MMWR Articles on Medical Devices
Review and coordination of revision of the CDC Condom Brochure

Table 11 – Ad-Hoc Post Market Surveillance Activities

Fetal Vacuum Extractors
YAG Laser Ablation
Cyanide Blood Levels after Laser Treatment of Uric Acid Stones
Oxygen Regulator
Inappropriate Interactions Between Pacemakers and Patient Monitors
AbTox Sterilizing System
Holmium Laser/Lithotripsy
EtO Exposure/Plasmapharesis and Dialyzer Patients
Hypersensitivity with Chlorhexidine Impregnated Cellulose Acetate Hemodialyzer
Telemetry/HDTV Interference Ad Hoc
Electronic Article Surveillance Systems (EAS)/Pacemaker Interactions
Heating Pad Fires
Operating Room Fires
Hazards Associated with Hospital Beds
Medical Issues Associated with Laser Pointers
Vacuum Loss in Electronic Components
Interaction Between Minute Ventilation Pacemakers & Bioelectrical Impedance Devices
Gamma Camera Failure Analysis
Excimer Laser Self-certification
Medical Device "Fires" Analysis
Systemic Technology Assessment of Medical Products (STAMP) Program

FORENSIC ANALYSES

Failure of a medical device in-service is seldom without significant adverse consequences to the patient on whom the device is being used at the time. Analyzing the failures and identifying the siblings of the failed device often require understanding the possible mechanisms of failure and deciding on an experimental approach while working with very little data. **Table 12** is an example of the forensic analyses performed this year. OST also provides several calibration services in direct support of CDRH, ORA, and state inspectors of radiation-emitting products. **Table 13** is a list of those calibration services and the numbers of devices from all calibrated sources.

Table 12 – Forensic Analyses

Degradation of Dialyzer Membranes – Chemical Analysis of Degradation Byproducts
Degradation of Dialyzer Membranes – Bioeffects of Cellulose Acetate Degradation
Degradation of Blood Filters – Chemical Analysis of Degradation Byproducts
Laser Pointers (10 samples)
Laser Rangefinder (2 samples)
Compact Fluorescent Lamp
Epilator (Electrical safety, flammability of insulating materials)

Table 13 - Instrument Calibrations

Diagnostic X-ray Probes - 1194
Mammography X-ray Probes - 248
KVp Meter - 92
Digaphots for the X-ray Standard - 78
Microwave Probes - 67
Laser Probes – 0 (laboratory out-of-service following move to 12725)

RESEARCH

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. The purpose of this directed research is to assist the regulatory program of the Center in anticipating the impact of technology on the safety, effectiveness, and use of regulated products. Research develops expertise and analyses for health risk assessments. The Office also develops new or improved measurement methods, techniques, instruments, and analytical procedures for evaluating product performance and reliability. OST provides innovative solutions to public health problems by developing generic techniques to enhance product safety and effectiveness. 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. As you can see from the **Table 14**, OST publications and presentations are a major output of the Office.

Table 14 - Deliverables from the Research Program

	1996	1997	1998
Journal Publications	61	48	52
Books & Chapters	12	7	5
Abstracts	78	65	76
OST Reports	-	8	5
Presentations	121	139	131

The following highlights reflect the several research programs of the Office.

BIOEFFECTS

A Model of Thermal Endometrial Ablation

Key words: endometrial ablation, modeling, tech support

Thermal endometrial ablation devices are designed to treat certain types of dysfunctional uterine bleeding, specifically menorrhagia (excessively heavy menstrual periods). Traditional treatments include hormone therapy and D&C (dilation and curettage). If these treatments fail, a hysterectomy may be necessary. However, nonsurgical alternatives to a hysterectomy are available in which only the endometrium (inner lining) of the uterus is destroyed and removed. These techniques are referred to as endometrial ablation. Two types of devices have been developed in recent years that locally ablate the endometrium -- transcervical endometrium resection devices and Nd-YAG laser ablation devices. A new generation of devices has been introduced to the market in the last year, which ablate the entire endometrium all at once by inserting a fluid-filled balloon catheter which heats the endometrium, thereby ablating the tissue responsible for menorrhagia. An analytical model of heat transfer into the uterine tissue is being developed that will help predict the effect of changes in the device operating parameters on tissue ablation.

The model uses a simplified geometry to generally predict the effects of heating temperature, time, and other physical properties of the device system on temperature distribution in the uterine tissue. The model assumes a relatively ellipsoidal uterus geometry which, when filled with fluid to an appropriate pressure, takes on the shape of a sphere. A spherical solution to the heat diffusion equation is used which takes into account energy removed from the tissue by the perfusion of blood in the uterus. The depth of ablation or other tissue effects can be predicted by considering the temperature elevation in the tissue.

At present the model is being used to advise the Center and the manufacturer of the potential for adverse effects resulting from changes in marketed device operating parameters. The model was compared with published results of temperature rise in the uterine tissue. Based on the comparison, a temperature rise of 48°C is required for tissue necrosis. Using 48°C as the critical temperature we can estimate how changes in operating parameters will effect the depth of necrosis. The model predicts that a difference of approximately 8°C in the inner surface temperature of the uterus results in a 1-millimeter increase in the depth of necrosis. The clinical significance of this change is under evaluation.

Testing of Radiofrequency Cardiac Ablation Devices

Key words: cardiac, ablation, arrhythmias, radiofrequency, RF, thrombus

Radiofrequency (RF) catheter ablation is a commonly used procedure for the management of cardiac arrhythmias. The procedure uses RF electrical energy delivered through one or several catheter electrode(s) to generate thermal lesions, which disrupt aberrant electrical pathways that cause potentially lethal cardiac arrhythmias. From 1989 to 1996, the number of cardiac ablation procedures performed annually in the United States has increased from 450 to approximately 25,000. There still remain many

unanswered questions regarding the procedures' safety and efficacy. CDRH is concerned about the different parameters affecting the development of lesion sizes, the extent of damage done in the myocardium, and the incidence of thrombus formation from catheter electrodes.

A new study in OST deals with the formation of thrombus and coagulum on catheters as a result of ablation. To date no formal studies have been conducted to characterize the energy dissipation of ablation catheters in turbulent blood-flow conditions. With the advent of higher power devices, the study of heat dissipation becomes increasingly important, as the dissipated heat may cause unanticipated damage to other tissue structures (e.g., heart valves). This issue has been recognized but not focused upon in the literature. The available literature, however, does suggest that new ablation devices that incorporate higher power energy delivery and are used in low flow conditions can produce a substantial amount of thrombus and coagulum, both of which increase the incidence of stroke in patients. This is due to heating of the blood near the ablation catheter tip to very high temperatures.

To study the issue of thrombus formation, OST constructed a specialized *in vitro* test system to measure near-electrode temperatures and heat transfer phenomena under near-physiologic conditions. This was done in order to simulate transient lesion development and describe the mechanisms that affect the safety and efficacy of ablation. The ablation evaluation system consists of three parts: a hydrodynamically controlled test chamber; a temperature probe (thermistor) array; and a variable radiofrequency source. A high-power radiofrequency (RF) amplifier and RF function generator are used in place of a commercial RF ablation generator to allow for maximum control over the signal waveform and power output. The test chamber produces laminar profiles for a viscous blood-simulating (phantom) material with hydrostatic pressures that simulate those found in the human cardiovascular system. The thermistor array is embedded in a tissue phantom material and can be configured to measure transient temperatures in the blood phantom downstream from the ablated area.

Risk Assessment-Based Approach for Systemic Toxicity Assessment

Key words: risk assessment, methods development

Systemic toxicity tests, as they are currently conducted for medical device materials, may have limited utility for regulatory decision making because of their inability to detect all but the most overt signs of toxicity. In addition, a lack of knowledge of the chemical constituents that are released from a device may lead to unfocused or unnecessary systemic toxicity testing. To address the limitations of the current approach, OST and ODE scientists are working to develop an extension of the existing approach for the assessment of systemic toxicity. The hallmarks of this approach are 1) identification of the compounds released from the device, 2) assessment of the dose of the compounds received by the patient, and 3) assessment of the risk posed by exposure to these compounds.

Before such an approach can be implemented, a number of significant scientific issues must be addressed, the most important of which is the development of science-based but practical thresholds for the detection and identification of compounds released from devices. During FY 98, OST scientists developed the scientific rationale for these thresholds. In addition, a number of risk assessment tools must be developed (see below) before such an approach can

be broadly implemented. Once this risk assessment methodology is developed, both Center scientists and submitters will have access to an approach that will provide information to better assess the potential for systemic toxicity to occur and will reduce unnecessary testing and animal use.

In-vitro Safety Studies of Cardiac Electrostimulation Devices

Key words: cardiac, stimulator, defibrillator

OST performs safety studies on medical devices implanted in the heart. This work applies to a number of devices which include the classic cardiac defibrillators (both implanted and external). The work concentrates on the possible deleterious effects of these devices upon live cells, and how these harmful effects can be avoided. In FY 98, work continued on the safety of electroshock from cardiac defibrillators.

Both automatic implanted cardioverter defibrillators (ICD) and the new pediatric use of automatic external defibrillators (AED) can generate local electric fields in the heart that are capable of inducing cellular dysfunction. Previous OST studies of heart cells have demonstrated that electroshock-induced dysfunction involves a prolonged calcium ion elevation in heart cells. The calcium elevation is associated with a period of refractoriness to pacing. Such cellular dysfunction is related to the production of secondary arrhythmias seen clinically following defibrillator shocks. For this calcium-related dysfunction, OST scientists determined its threshold, relationship to shock strength, relationship to shock waveform, and the cell locale of the effect.

During FY 98 OST scientists focused on the possible interaction of this event with pharmacological agents. First, they demonstrated that the shock-induced calcium elevation is caused by both calcium entry through the cell membrane and by release from intracellular stores. Second, they demonstrated that the cardiac drug verapamil (an L-type calcium channel blocker) reduces most of the prolonged calcium elevation, but it does not abolish the associated refractoriness to pacing (see **figure 1**]). These experiments were performed on excised heart cells maintained in culture, stained with a calcium-sensitive dye and shocked with defibrillation pulses. The defibrillation shock of 56 volts/centimeter is presented to the cell after 10 seconds in each of the three illustrated trials. In normal media (upper trace), regular calcium action potentials are converted to a prolonged calcium elevation by the defibrillation shock given at 10 seconds. The calcium channel-blocking drug (verapamil, middle trace) nearly eliminates the prolonged calcium entry. This effect is reversible with drug washout (lower trace). A low-noise, cooled CCD camera recorded the calcium-related intracellular fluorescence changes. Results from this work have served in establishing review criteria for a number of medical devices.

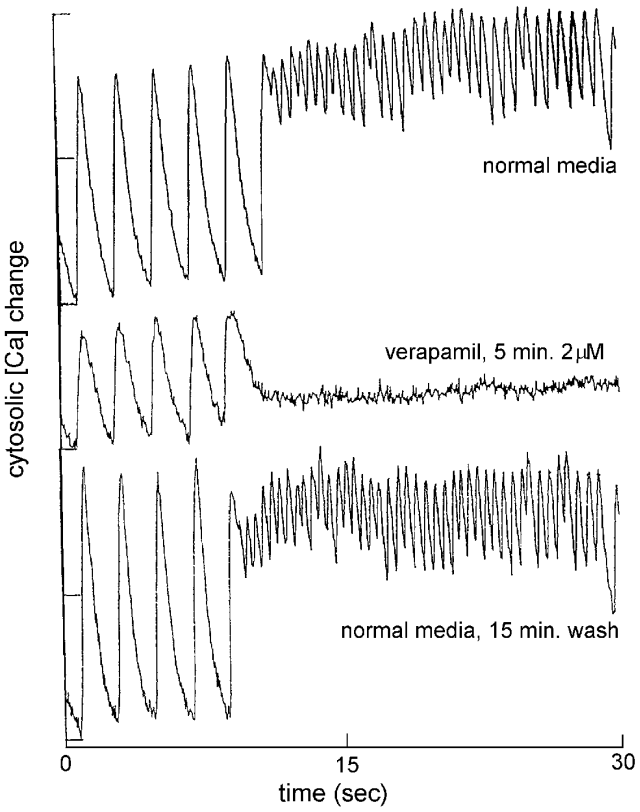

Figure 1. Calcium channel-blocking drug reduces calcium entry following a high-voltage defibrillation shock in heart cell. The defibrillation shock of 56 volts/centimeter is presented to the cell after 10 seconds in each of the three illustrated trials. In normal media (upper trace), regular calcium action potentials are converted to a prolonged calcium elevation by the defibrillation shock given at 10 seconds. The calcium channel blocking drug, verapamil (middle trace), nearly eliminates the prolonged calcium entry. This effect is reversible with drug washout (lower trace).

In-vitro Safety Studies of Nerve Electrostimulation Devices and Biosensors

Key words: neurology, stimulator, biosensor

OST performs safety studies on medical devices implanted in tissues of the nervous system. This work applies to a large number of devices that include brain stimulators, spinal cord stimulators, and peripheral nerve stimulators, as well as a new series implants which require nerve growth onto bioactive surfaces. The work concentrates on the possible deleterious effects of these devices upon live cells and how these harmful effects can be avoided. Over the past fiscal year an effort in the area of cell-based biosensors was also initiated.

A related area of investigation is a proactive study of engineered surfaces for nerve cell and heart cells growth. A new generation of medical devices will use coatings and surfaces designed to promote interaction with the nervous system or serve as scaffolding for heart cells for tissue replacement. Moreover, ordered arrays of synaptically connected nerve cells would serve as biosensors for bioeffects from medical devices or the presence of neurotoxic substances. Hence, a collaborative study is being performed with the Johns Hopkins University Applied Physics Lab and George Washington University Department of Chemistry, which involves the growth and survival of explanted neurons on surfaces coated with different biopolymers. Work has demonstrated that electrophysiological

features of heart cells depend upon the chemical composition of the growth surface. In-house co-culturing techniques of retinal ganglion neurons and brain neurons from adult goldfish have been established. Preliminary work shows that these nerve cells form networks in culture. In-house techniques for culturing embryonic neurons from rat hippocampus have also been developed. This cell technology, in conjunction with techniques for optical and electrical recording from cells, will be used as the basis for biosensor arrays for detection of harmful effects or substances from medical devices. This collaborative work is being supported by a grant from the Department of Energy for biosensor development.

Design and Synthesis of Peptide Nucleic Acids Specific to Genetic Sequences of *Mycobacterium Tuberculosis* (M.tb)

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

An OST molecular biologist and collaborators from FDA's Center for Biologics and Research have designed and synthesized several different types of peptide nucleic acids (PNAs) that hybridize, or bind, with selected genetic (DNA) sequences of M.tb, the causative agent of tuberculosis. DNA molecules are commonly used in medical areas of molecular *in vitro* diagnostics and molecular pathology as biochemical probes to detect the nucleic acids (DNA or RNA) of infectious microorganisms. The DNA probes are designed to hybridize specifically with the viral or bacterial nucleic acids that one wants to detect, and sensitive biochemical methods such as gel electrophoresis combined with radioactive or fluorescent dye labeling of the probes can be used to identify these nucleic acid hybrids.

Recently, PNA molecules, which are chemical strands that contain DNA bases attached to a protein-like (peptide) structural "backbone," have become available to the scientific community. PNAs are unique in that they have enhanced physical and chemical characteristics as probes for molecular diagnostics, because they have higher thermal stability and greater binding specificity as compared with DNA molecules. They can be used in combination with the well-known and already sensitive molecular detection method polymerase chain reaction (PCR) for the specific and highly sensitive detection of mutant nucleic acids. The PNAs synthesized by the FDA scientists were designed such that some of them will hybridize with the sequences of genes associated with antibiotic drug-resistance genes of the wild-type strain of M.tb; others will hybridize with sequences of certain mutants of the drug-resistance genes.

The long-range plan of this research is to attempt using the PNAs to develop a rapid diagnostic procedure for the detection and identification of drug-resistant strains of M.tb. The emergence of a variety of antibiotic drug-resistant strains of Mycobacterium tuberculosis (M.tb) has caused a serious health problem world-wide, and rapid diagnostic procedures are needed for the detection of these M.tb mutant strains. In addition, the laboratory experience gained from this project should enable us to make informed premarket evaluations of commercial molecular *in vitro* diagnostic devices used for the detection of wild-type and mutant strains of M.tb.

Impact of Human Genetics on Product Safety Evaluation and Adverse Events

Key words: human genetic diagnostics, genetic variability, adverse response susceptibility, latex allergy, cancer.

The scientific revolution in human genetics will have many consequences, including the nature and number of diagnostic products submitted to the agency. However, the new information provides new tools for biological safety evaluation of FDA-regulated products and new ways to consider postmarket adverse events. Several avenues under exploration in OST are described below.

Genetic variations within the "normal" range in humans are being catalogued world-wide and related to exceptional susceptibility or resistance to disease, including cancer, autoimmune disease, and cardiovascular disease, among many others. Some of these variations will cause a disproportionate adverse response to medical device materials. A candidate example is latex allergies, which affect a substantial minority of people exposed to the protein in latex gloves. OST scientists are searching for candidate genetic polymorphisms that could be related to latex allergies. Identification of genetic susceptibility factors related to latex allergy would be a major step in understanding the process and would aid in identifying individuals who should avoid excessive exposure to latex products.

Substances that damage DNA are related causally to the development of cancer, but there is one other probable adverse consequence for which data are lacking: the induction of heritable mutations causing genetic disease. Experiments in animals have shown that DNA-damaging agents do cause mutations in the germ cells that are manifested in the next generation. Circumstantial evidence consists of quite a substantial rate of human spontaneous fetal loss and the finding of visible chromosomal damage in many of these. Approximately 1% of newborns have some type of genetic or developmental anomaly. While environmental exposures (e.g. thalidomide) have been linked in some cases to developmental disease, there is no case of an environmental exposure being associated with a genetic disease.

The situation is complicated by the existence of a substantial proportion of *inherited* genetic disease (e.g. cystic fibrosis), i.e. mutational alterations that are pre-existing in a previous generation, the frequency of which varies greatly with different diseases. New genetic technologies now make it feasible to identify the precise nature of genetic alterations in patients, determining whether the genetic disease is newly arising or pre-existing, and using this and other information to relate disease outcomes in individuals to external exposures. The application of these new technologies will help determine whether induction of human genetic disease is a second DNA-damage related adverse event that should be considered in the safety evaluation of products.

Large Animal Cardiovascular Research Program

Key words: cardiovascular, implants, animal science, vascular disease

CDRH has established a large animal cardiovascular research program to develop and study models of cardiovascular disease, vascular injury, and long-term vascular implant performance. This research brings together an interdisciplinary group of both Government and non-Government scientists and clinicians with expertise in

cardiovascular physiology and pharmacology; radiology; pathology; cardiology; animal science (swine), tissue biomechanics, and the molecular biology of vascular disease. The laboratory, which is sited at the FDA's Center for Veterinary Medicine in Laurel, Maryland, can be used for animals ranging from rodents to full-size swine. The 1,200 sq. ft. of dedicated laboratory space includes a small animal procedural lab, wet lab, gross pathology lab, *in vitro* physiology lab, and an interventional radiology/surgery suite. The interventional radiology suite allows performance of diagnostic angiography as well as interventional procedures (e.g., balloon angioplasty, stent placement, and selective catheterization) under sterile conditions with general anesthesia.

The regulation of devices for the diagnosis or treatment of cardiovascular disease is a major component of the Center's effort. For example, human studies of devices that pose a significant risk to the patient require application to the FDA for approval of the study. Between 50-60% of these applications are for study of cardiovascular devices. Pre-clinical animal studies of full-size devices are typically required prior to approval of an IDE application and progression into clinical trials.

OST scientists in collaboration with their counterparts in ODE are currently studying the effects of gender and hormonal state on the function and mechanical properties of coronary arteries and on the healing response of arteries to balloon injury under a grant funded by the FDA's Office of Women's Health. The motivation for the study is the observed greater incidence of cardiovascular death in postmenopausal women and in men of all ages compared to premenopausal women. There is epidemiological evidence that estrogen replacement therapy in postmenopausal women provides some protection against coronary artery disease. The proliferative response of an artery following angioplasty, a major cause of restenosis following this treatment, may also be reduced by estrogen therapy.

In this study, the effects of balloon injury of the coronary artery and acute ischemic insult to the heart are evaluated in a swine model representing permutations of gender and hormonal state. The left anterior descending coronary artery is injured by balloon dilation, as in the treatment of coronary artery disease, which results in a proliferative response by the vessel wall. One month later, the coronary blood flow is directly measured and evaluated for changes in response to temporary complete occlusion of the artery. Samples of the coronary artery are collected for *in vitro* measurement of biomechanical properties and smooth muscle contractility. Complete histopathological study of the injured site is performed. In addition, samples of the peripheral arteries are collected for similar study of the biomechanical properties. Samples are also collected for study of differences in expression of genes relevant to normal and abnormal function of the vascular wall.

The project addresses gender and hormonal influences on hemodynamic, biomechanical, pathological, and molecular parameters of normal vascular function as well as the response of the vasculature to injury. The results should shed light on gender and hormonal differences in the progression and treatment of cardiovascular disease in humans. This project will also result in a better definition of the pre-clinical (animal) testing which should be conducted prior to testing of the cardiovascular devices in humans.

BIOEFFECTS-RADIATION

Biological Effects of Exposure to Electric and Magnetic Fields (EMF)

Key words: EMF, molecular biology, biological effects

Health issues concerning exposure to electric and magnetic fields (EMF) are discussed extensively in the news. There are a number of products under the regulatory authority of FDA which emit or utilize EMF radiation. These include electric blankets, video display terminals, and medical devices such as those used to treat non-unions (bone fractures), as well as wireless communications devices such as cellular telephones. Concern stems, in part, from epidemiological reports suggesting that power line frequency EMF may play a role in cancer promotion. The program described below is part of a national research effort with contributions from NIH, CDC, DOE, and FDA. The data from this research will be used in an NIH risk-analysis process leading to a Congressional report. This will place the FDA in a better position to evaluate the safety claims of products emitting power line frequency EMF. The principal objectives of the program are (1) to establish and maintain a regional *in vitro* magnetic field exposure facility and (2) to perform studies which address the issue of reproducibility of published power line frequency EMF biological effects. NIH and the FDA supported this program. During FY 98, this program produced nine published abstracts, one published full-length paper, and nine research presentations at scientific meetings.

A state of the art, regional EMF exposure facility was developed. The two systems that comprise the core of this facility are capable of exposing samples to environmentally relevant power line frequency magnetic fields. They have been used for the work described below, as well as for research performed in collaboration with non-FDA investigators.

1. EMF and Gene Expression *In Vitro*

Key words: EMF, molecular biology, oncogenes, heat shock

This project (see program description above) has addressed the issue of cancer promotion through investigation of the effects of power line frequency (60 Hz) EMF exposure on gene expression. Specifically, the effect of such EMF exposure on gene expression in human leukemia cells has been analyzed by screening for changes in steady state levels of specific messenger RNAs. This study also addresses the issues of repeatability and accuracy of published research. Specifically, it includes a replication of the published experiments that were performed to conclude that the expression of the *MYC* proto-oncogene is increased when cells are exposed to 60-Hz EMF.

A detailed protocol for the gene expression replication study was developed in collaboration with the original investigators and peer-reviewed by a panel of experts. Control baseline studies performed to determine the precision and accuracy of the assay methods demonstrated that these methods were suitable for detecting reproducible changes in gene expression of greater than 10%. Positive control studies provided a frame of reference for the magnitude of signals observed in the presence of EMF and demonstrated that the assay system was responsive to experimental perturbations. Replication experiments showed that *MYC* gene expression in EMF-exposed cells was

not distinguishable from that in sham-exposed cells, thus seriously questioning the conclusions of publications positing an EMF exposure-associated change in *MYC* gene expression. This work was published in *Radiation Research* as a full-length article and accompanied by an editorial emphasizing the importance of publishing carefully conducted replication studies such as the work described above.

Several presentations purporting to have clarified an effect of EMF on *MYC* expression have been made at past scientific meetings. Indeed, these presentations were published as abbreviated reports in the scientific literature. To address such claims and to confirm and extend the results of the work described above, OST investigated changes in *MYC* gene expression under conditions that spanned a wide range of exposure times and intensities. In addition, these experiments were conducted using multiple cell lines. These factors were critical to the claims made in the presentations mentioned above. The results of the OST studies clearly demonstrated that claims of an effect of EMF on *MYC* expression made at scientific meetings were based on insufficient evidence.

Recently, there have been reports that exposure to power line frequency EMF is a cellular stress sufficient to induce heat shock protein messenger RNA expression and DNA-binding activity. To address the accuracy and reproducibility of these reports, OST measured the response of heat shock gene messenger RNA levels to carefully controlled power line frequency EMF exposures.

2. EMF and Enzyme Activity

Key words: EMF, biochemistry, ODC

This project is a continuing effort investigating the effect of 60-Hz magnetic fields on cellular processes related to proliferation and tumor promotion. This project (see program description above) has addressed the issue of cancer promotion through investigation of the effects of 60-Hz EMF exposure on enzyme activity. Specifically, the effect of EMF exposure on enzyme activity in mammalian cells has been analyzed by screening for changes in the activity of ornithine decarboxylase (ODC), an important marker for cell proliferation and tumor promotion. Our previous work has indicated that it is in fact not possible to replicate one of the major reported effects of magnetic fields on ornithine decarboxylase (ODC). Our finding that the earlier data are suspect further strengthens the findings of the National Academy of Sciences committee that magnetic field exposure is not a cause of childhood leukemia. During the past year, we have extended our earlier *in vitro* experiments on ODC activity to experiments involving live rodents chronically exposed to various magnetic fields intended to simulate those found in the human environment.

During FY 98, OST participated in a collaborative effort to replicate a more recently reported finding that magnetic field exposure induces ornithine decarboxylase activity in rats exposed *in vivo* previous studies have suggested that ODC activity is increased in several tissues of rats exposed to power frequency magnetic fields; these results suggest a possible role for environmental magnetic fields in cancer etiology. It is important to note, however, that environmental magnetic fields often contain not only a 50- or 60-Hz waveform, but also a series of higher harmonics that are superimposed on the underlying signal. The goal of the present study was to determine the effect of pure 60-Hz magnetic fields and higher harmonics on ODC activity, a biochemical endpoint whose induction has

been used as a marker for tumor promotion. Exposure groups included 1) ambient magnetic fields only; 2) pure 60 Hz magnetic fields at 2.0 G; 3) pure 180-Hz magnetic fields at 2.0 G; 4) 60 Hz magnetic fields with superimposed 3rd harmonic (10%), total field strength = 2.0 G; and 5) 60-Hz magnetic fields with superimposed 3rd (35%), 5th (10%), and 7th (5%) harmonics, total field strength = 2.0 G. Rats received magnetic field or sham exposure for 18.5 hours per day for 4 weeks. Ten treatment group comparisons were performed for each of four tissues from each of four participating laboratories; from these comparisons, only two instances of statistical significance emerged. Data from one laboratory indicated that brains from rats exposed to 180-Hz magnetic fields demonstrated significantly higher ODC activity than did brains from rats in all other groups, including sham controls. This finding was not replicated by the other three laboratories, and no overall pattern of elevated ODC activity was seen for this tissue and exposure group.

Other exposure conditions examined during this collaborative study included randomly time-varying 60-Hz magnetic fields (0.02 to 2.0 G); intermittent 60-Hz magnetic fields (2.0 G; 5 second on/off); intermittent 60-Hz magnetic fields (2.0 G; 15 second on/off); intermittent 60-Hz magnetic fields (2.0 G; 300 second on/off); pure 180-Hz (3rd harmonic) magnetic fields at 2.0 G; 60-Hz magnetic fields at 2.0 G with superimposed transients; and randomly time-varying 60-Hz magnetic fields (0.02 to 2.0 G) with superimposed transients. As in the harmonic study, no overall pattern of elevated ODC activity was seen for any tissue or exposure group.

In addition to these *in vivo* studies in rodents, OST also tried to replicate a reported enhancement of ODC activity in developing chick embryos after exposure to 40-mG, 60-Hz magnetic fields during gastrulation. Six experiments were conducted at 15, 18, 23, and 28 hours of exposure to the magnetic fields, followed by harvesting the embryos for ODC assay. Although researchers observed the reported variations of ODC activity with incubation time, they did not observe any statistically significant enhancement of ODC activity due to field exposure.

Magnetic Resonance Imaging Safety- RF Heating of Patients

Key words: MRI, safety, SAR, magnetic fields

Magnetic Resonance Imaging (MRI) has become a very widely used medical procedure. Closed and open systems are typically used with static magnetic fields at or below 2 Tesla. High-field MRI devices ranging from 3 Tesla to 8 Tesla are now being used in clinical investigations with patients. Manufacturers of these high-field systems are submitting claims that their devices are safe and effective. This project concentrates on the patient-safety issues of MRI due to the strong radio frequency (RF) magnetic field produced by any MRI device. The RF magnetic field deposits RF energy in the patient's body resulting in potentially dangerous heating of certain areas of the body. The parameter known as Specific Absorption Rate (SAR) is a quantitative measure of this energy absorption. The use of metallic medical devices in contact with the patient's body causes an increase in the RF energy deposition in the body. This is especially true for devices with leads implanted in the body.

An in-house project was initiated in FY 98 to calculate the SAR throughout a realistic computer-model of the human body exposed to RF magnetic fields similar to those from a typical MRI device. The human body model is made of a mesh composed of cubic

elements, each being as small as 5 millimeters on a side, and having the RF electrical properties of the body tissue type it represents. A model of a man derived from the National Library of Medicine (NLM) Visible Human Project and a model representing the partial body of a woman developed at the Catholic University, Washington, DC, are used for this study. A commercially available electromagnetic field analysis program (Remcom XFDTD) based on the finite difference time domain (FDTD) method is used to calculate the electromagnetic fields and SAR distributions in the human bodies by solving the electromagnetic field problem in the time domain. Calculation of SAR distributions in the male and female models were performed using 64 MHz and 340 MHz plane wave sources as well as sources simulating RF magnetic fields from an MRI body coil (developed at the Catholic University) in a 1.5 Tesla and an 8 Tesla device. The 1.5 Tesla and the 8 Tesla devices produce, respectively, 64 MHz and 340 MHz RF magnetic fields.

Preliminary results indicate much greater absorption of RF energy in the patient tissues and deeper penetration of RF into the body from the 8 Tesla device versus the 2 Tesla device. The SAR distributions in the patient tissues from both MRI devices are highly nonuniform. The results indicate that the use of a proper human model, with realistic simulation of the RF magnetic fields produced by the MRI body coil rather than a plane wave, are necessary. Additional SAR calculations are also needed to determine the RF energy absorption in patient's bodies due to the contact of metallic devices with the patient.

Reassessing the Safety Issues in Using UV-Emitting Devices and Photosensitizing Drugs for Patients with HIV Infection

Key words: photomedicine, ultraviolet radiation, photosensitizing drugs, HIV, AIDS, bioeffect

OST previously concluded that, in spite of some outstanding clinical and scientific questions, there was no need for an FDA action that would restrict or modify using UV-devices in the treatment of skin diseases in HIV-infected patients. In the meantime, new therapies employing multiple drugs became commonly available. This substantially altered the clinical course of HIV infection, including HIV infection-related skin disorders. Also, new clinical data became available on the use of UVB therapy in HIV patients. For these reasons, OST reassessed the safety issues related to the use of UV-emitting devices (and photosensitizing drugs) for patients with HIV infection. The results have been published in an invited editorial article in Archives of Dermatology. Briefly, the available data indicate that UVB therapy can activate HIV locally in the skin; however the systemic viral burden does not change under these circumstances. This is most likely related to the fact that the amount of the virus in the skin is low relative to the total viral burden in the body. Although no similar direct evidence is available for PUVA (8-methoxypsoralen plus UVA) therapy, clinical observations suggest few adverse effects of the latter therapy. Thus, the OST position on the safety of UV therapies in HIV infection remains unchanged.

Risks and Benefits of Exposure to Ultraviolet Radiation

Key words: photobiology, photomedicine, UV, photosensitizing

Current FDA policies regarding sunlamps were first developed in 1979 and then revised in 1986. Since then, photobiology and photomedicine have progressed substantially. Understanding of the risks and benefits of exposure to ultraviolet radiation now includes new facts about UV-induced cancer, UV-induced immunosuppression, limited protection by pigmentation, etc. At the same time, tanning industry has grown to serve approximately 25 million Americans. Under these circumstances, FDA received a Citizen's Petition requesting eleven different actions that, as the petitioner suggests, would improve the safety of the use of artificial tanning devices, sunscreens, cosmetics, and photosensitizing medications.

To review the current status of knowledge in this area, OST organized a workshop titled "UV: Accessory to Melanoma - If So, How?" at the meeting of the American Society for Photobiology in July 1998 and included appropriate topics into the agenda of the International Symposium and Workshop on Measurements of Optical Radiation Hazards in September 1998. Collaborating with the National Institutes of Health, under the auspices of the Skin Disease Interagency Coordinating Committee, OST organized the research workshop titled "Risks and Benefits of Exposure to Ultraviolet Radiation and Tanning" attended by the leading experts from the U.S., Australia, France, Germany, Sweden, The Netherlands, U.K., and other countries. The body of knowledge reviewed at these three meetings allowed OST scientists to prepare a response to the Citizen's Petition and to decide that the FDA Sunlamp Performance Standard should be amended with changes in the exposure schedules, warning labeling, etc,

Simultaneously, OST continued to work with the Commission Internationale de l'Eclairage (CIE) on the standards for action spectra for UV-induced cancer, and for protocols for testing of cancer induction by UV. OST was invited by the CIE to lead a new effort aimed at the selection of typical minimal erythema doses for persons with different skin types. Further, OST scientists initiated attempts to harmonize the FDA Sunlamp Standard with an equivalent standard of the International Electrotechnical Commission (IEC).

Most current standards have been developed for one skin type only, and no adjustments for different UV sensitivities have been introduced. In the process of analyzing of these standards and the available information, we realized that the actual responses of the human skin to UV have never been properly standardized. Such standardization would aid the practices and policies not only in the areas of artificial tanning devices, sunscreens, cosmetics, and photosensitizing medications but also in the clinical applications of UV. For this reason, we took part in the development of a new research program titled "Quantitative, Biologically Relevant Parameters for Testing and Standardization of Skin Response to UV." This program has been selected to be funded by the FDA Office for Science. The program has been developed within the FDA Photosciences Network and involves CDRH, CDER, CFSAN, and NCTR. It is expected that the results of this study will support [or facilitate development of new] FDA policies related to the sunlamp products, sunscreens, cosmetics, as well as phototoxic and photocarcinogenic properties of some drugs.

ELECTROMAGNETIC INTERFERENCE

Magnetic Field Symmetry Around Candidate Dipoles for AAMI Pacemaker EMC Testing

Key words: AAMI, pacemaker, electromagnetic compatibility, dipole, cellular phone, interference

OST has been involved for many years in the testing of implanted cardiac pacemakers and defibrillators for susceptibility to electromagnetic interference from nearby radiofrequency (RF) emitters, such as cellular phones. OST staff were directly involved in the translation of their work into a standardized testing method. This was done through involvement with a working group that is developing a pacemaker/cellular phone EMC test method under the auspices of the Association for the Advancement in Medical Instrumentation (AAMI).

In prior years, OST demonstrated a method for substituting a standard dipole antenna and a laboratory RF generator for a cellular phone as an emitter of RF magnetic fields. The draft AAMI standard specifies the use of dipoles instead of actual cellular phones. It also requires that the dipole antennas be well characterized in terms of the magnetic field distribution very close to these simulated cellular phone antennas. An evaluation of the fields close to dipole antennas from any various commercial sources is an important part of the foundation of the AAMI test method. Data from this type of evaluation will enable those who test pacemakers using the AAMI method to obtain reasonably valid results that can be repeated in another laboratory using a different manufacturer's dipole.

Five dipoles were measured, three at 850 MHz and two at 1850 MHz., and the symmetry of the fields produced by the antennas was evaluated. The saline-filled tank and test grid, already proposed for pacemaker EMC testing, were supported by foam blocks that placed the floor 76 centimeters below the test grid. A computer-controlled XY-scanner was positioned 66 centimeters above the test grid. A fiberglass arm was attached to the moveable car of the XY-scanner. The fiberglass arm held the H-field probe level with the dipole arms. The tank was filled with 0.18% saline to 2.0 centimeters below the arms of the dipole. The separation between the dipole arms and the center of the H-field loop was 2.5 centimeters (**figure 2**). The dipole was held on a vertical test grid with nylon tie-wraps. The H-field probe consisted of a loop, 1.5 centimeters in diameter, formed from semi-rigid coax with a 1-mm ring of outer conductor removed at the distal end of the loop. The middle of each dipole's arms was found visually and considered the center point for each scan. Measurements were made every millimeter along the axis of the dipole's arms from 3 centimeters beyond the left tip to 3 centimeters beyond the right tip.

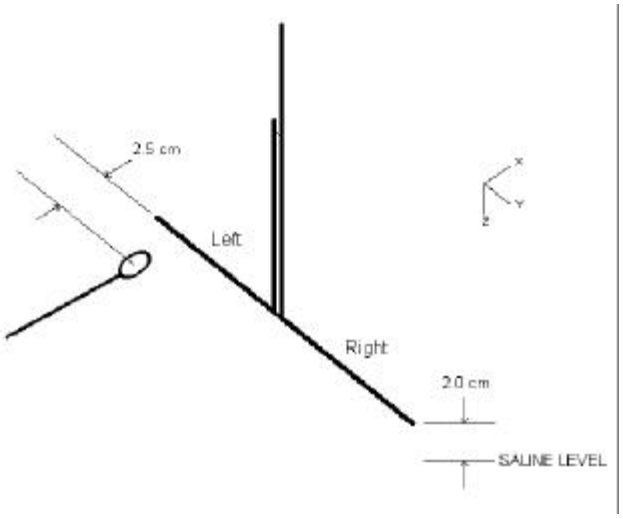

Figure 2. Separation between dipole arms and center of H-field loop

The output of the signal source was split by a directional coupler. One of the coupler's outputs was connected to the reference input of a network analyzer while the other was connected to the dipole under test. The H-field probe was connected to the test input of the network analyzer. A laboratory PC controlled the scanning motion and read the output of the network analyzer at each test point. The data from each scan was analyzed by a left-to-right correlation technique that found the center point yielding the best symmetry. In all cases this center point was within 2 millimeters of the position visually identified as the middle of the antenna.

For all five antennas, the imbalance was less than 0.5 dB within the –3 dB points of the antenna. For EMC tests using the dipoles to simulate wireless communications devices, the device under test should be positioned within the -3 dB points to insure consistent test results. The draft AAMI standard does not specify either a horizontal or a vertical orientation for this test. This specification should be written to reduce variability in test results among future users of the proposed test method. Continuing efforts will focus on fully validating the test system, performing measurements in both the vertical and horizontal orientation, automating testing procedures, and publishing the results.

Laboratory Studies on Electronic Article Surveillance (EAS) Systems and Metal Detectors as Sources of Interference with Implanted Medical Devices

Key words: magnetic field, electronic article surveillance systems, electromagnetic interference, implanted devices

OST engineers have completed electric and magnetic field mapping of eight electronic article surveillance systems (EASS), and a detailed internal report is being prepared on this project. The results of these measurements were presented at a public meeting of the Technical Electronic Product Safety Standards Committee (TEPRSSC) in conjunction with a discussion on the risks associated with exposures of personnel to EASS magnetic fields. These risks included interference with the proper operation of implanted medical devices such as cardiac pacemakers and defibrillators and spinal cord stimulators.

A testing protocol for evaluating interactions of EAS systems with medical devices was developed in OST. A simple rectangular model of a human torso (phantom) was built,

and preliminary testing on a pacemaker was performed. Currently phantoms used to test implanted medical devices for interference from EAS systems are composed of saline (as a tissue-simulating material) in a plastic or glass container. Some concern has been raised about the appropriateness of the particular shape and composition of phantoms and how to correlate test results performed in phantoms with published clinical studies using human subjects. This protocol, the phantom, and the necessary instrumentation are now available to be used to evaluate the effectiveness of interactions as compared with data from recent clinical studies of EAS interference with medical devices.

Electromagnetic Interference with Medical Telemetry

Key words: electromagnetic interference, medical telemetry, EMI

Wireless medical telemetry is primarily used to transmit, via radio signals, important physiological information from patients to monitoring stations in the hospital. In March 1998, a TV station in Dallas began broadcasting a newly authorized digital TV (DTV) signal on a previously vacant TV channel. The vacant TV channel was being used by two local hospitals for medical telemetry purposes as authorized under FCC rules. The DTV signal overwhelmed the telemetry signals of over 60 patients in these hospitals. Quick work by the engineering staff of the hospitals avoided injury of any patients. The incident clearly demonstrated the vulnerability of wireless medical telemetry to EMI. This incident triggered actions by FDA, the Federal Communications Commission (FCC), the American Hospital Association (AHA), and device manufacturers to address the very real potential for patient consequences from EMI. Upon hearing of the Dallas incident, OST worked to help develop a Public Health advisory warning wireless medical telemetry users of the potential for EMI from DTV signals. The FDA Advisory summarized the Dallas incident and recommended coordination with local TV broadcasters and the FCC to avoid further occurrences. In addition, OST engineers coordinated the FDA advisory with public announcements by FCC to address the concerns. FCC took further steps to minimize the reoccurrence of interference with wireless telemetry from the new DTV signals by requiring licensed broadcasters to make efforts to contact local health care facilities prior to broadcast.

At the present time, wireless medical telemetry is assigned a secondary status by the FCC for use with specific frequencies, such as unused TV channels and Private Land Mobile Radio Service (PLMRS). This means that wireless medical telemetry may not cause any interference to the primary, licensed users of the frequencies and must accept interference. OST presented its concerns about EMI and medical telemetry, and its plans for addressing these concerns, at the public meeting of the Technical Electronic Product Safety Standard Committee (TEPRSSC), an advisory panel for radiological health under the Radiation Control for Health and Safety Act of 1968. The TEPRSSC expressed support for CDRH's efforts to seek primary status and dedicated frequencies for medical telemetry. Toward that end, OST engineers have been active participants in the AHA Task Force on Medical Telemetry, constituted under the auspices of AHA to address the issue of EMI with medical telemetry. This AHA task force is working with the FDA and FCC to obtain primary-use frequencies for wireless medical telemetry.

Compatibility of Medical Devices with Magnetic Resonance Radiofrequency Fields

Key words: magnetic resonance imaging, medical devices, safety, compatibility radiofrequency

With the advent of interventional magnetic resonance (MR) imaging, the realm of medical devices required to function properly in this environment has expanded to include virtually any device from surgical instruments, such as scalpels and needles, to more complex and active devices, such as ventilators and anesthesia machines. As a result, there is a steady increase in premarket submissions with claims that devices are safe and effective in the MR environment. There are currently no accepted standardized test methods for determining the safety and effectiveness of a device in the MR environment. Therefore, OST has established an in-house facility for exposing medical devices to the harsh radiofrequency (RF) fields present during MR and is developing test procedures in harmony with recently initiated MR standards efforts in ASTM. The components of the MR RF Field Simulation system have been integrated and installed in the new MR laboratory. The heart of the system is the radio frequency body coil, a custom built "bird cage"coil similar in design to those used in actual MR systems. The MR RF Coil was tuned to a resonant frequency of 63.8 MHz. This resonant frequency (Larmor frequency) corresponds to an MR system with a 1.5 T static field magnet, which is one of the most common systems in use today. Preliminary low power spatial mapping of the coil revealed a uniform magnetic field distribution within +/- 2 dB over the critical volume of the coil.

The MRI RF simulator operates as follows. A low-level RF signal (-7dBm) is generated by modulating a 63.8 MHz RF signal with a 3-microsecond sinc pulse using an RF mixer. This low-level signal is fed into the RF input port of a 20 kW (peak power) Erbtec MRI RF amplifier. The amplifier was tuned to produce approximately 50 dB gain at 63.8 MHz. Circuitry was designed and constructed to provide the amplifier with the pulse enable signals necessary for the device to function independent of a complete MR system. A safety interlock was designed to shut down RF in the event that the chamber door containing the RF coil is opened.

In addition to the laboratory work, support has been provided to other Offices in CDRH on the scientific reviews of safety and effectiveness claims of devices in the MR environment. This work has continued to increase in volume significantly from previous years. The guidance document entitled, "A Primer on Medical Device Interactions with Magnetic Resonance Imaging Systems" has been revised to consider all comments received and is in the formalized guidance process for becoming a final guidance document. The Magnetic Resonance Working Group continues working cooperatively to address the Center's needs with regard to MR Compatibility and Safety issues.

IMAGING

Advanced Problems in Statistical Classification and Estimation

Key words: signal detection theory, assessment, neural networks, pattern recognition, CADx, research

There are at least three problems in diagnostic medicine that have similar statistical structure. The first is the problem of reconstruction of images from incomplete data sets. In practice, any sampled image data set is incomplete, so this first problem is in fact the general problem of image formation and estimation. The second problem is the detection and classification of disease from a finite set of diagnostic tests, features, or images. This problem is referred to as the problem of statistical pattern recognition. The third problem is that of assessing the performance of systems used for image formation, estimation, and disease classification. Scientists in OST are engaged in an active research program on the statistical properties of these related problems and their various solutions.

In the past year OST scientists have continued their investigations of images reconstructed from sparse data (fast imaging systems) based on neural network and other algorithmic observers, which was reported on at the annual SPIE Medical Imaging Conference in San Diego in February 1998. Because of their expertise in neural networks, OST staff have key leadership roles, including General Chair and Vice General Chair, in planning and preparing for the International Joint Conference on Neural Networks (IJCNN'99). IJCNN'99 is the primary international conference on advanced methods of computational intelligence and will be held in Washington, DC, in July 1999. It places major emphasis on biomedical applications of these technologies and on their relationship to classical statistical methods.

OST scientists are also pursuing approaches to the analysis of a limited number of diagnostic tests or images for several diagnostic modalities. OST has developed, tested, and published a theoretical framework which models the statistical properties of lesion detectability in medical ultrasound. This work has been submitted for publication and is also the basis of a draft AIUM (American Institute of Ultrasound in Medicine) standard for a phantom-based measurement methodology to assess medical ultrasonic imaging system performance (including lesion detectability).

Recent research on algorithmic observers for image assessment is converging with the work on computer-aided diagnosis for two reasons: the similarity of the approaches; and the importance of image quality for image-based computer-aided diagnosis. At the annual SPIE Medical Imaging Conference in San Diego, OST scientists reported on the statistical properties of some model observers used for image quality assessment. This work was extended for several workshops presented during the summer of 1998, and at the First International Conference on Computer-Aided Diagnosis at the University of Chicago in September, OST provided an overview of the problem of designing model observers for image quality assessment, model observers for computer-aided diagnosis, and the convergence of these problems.

Assessment of Classical and Neural-Net Classifiers

Key words: neural network classifiers, variance

Classical and neural-network classifiers are used in new modalities for computer-assisted reading of medical images and computer-aided fusion of diagnostic tests. Investigators in the Medical Imaging and Computer Applications Branch, in a collaboration with investigators at the University of Michigan Radiology Department, have been studying the statistical properties of these modalities, in particular the biases and variances of classifier performance assessment in the context of finite training sets and finite test sets.

Several reports on this work have been published this year. Principal results include polynomial models for the bias and variance, and the use of statistical resampling strategies to estimate the relative strengths of the various components of variance (training sample size, test sample size, and their interaction).

Mammography

Key words: mammography, phantom, dosimetry, thermoluminescent dosimetry, tissue-equivalence.

OST staff continued to investigate the clinical potential of the optimized mammography system (OMS) that has been developed by CDRH in collaboration with the University of Southern California and the Clinical Center at NIH. During FY 98, additional progress was made in developing a protocol for the clinical evaluation of the optimized system in its original, low-dose configuration. The planned protocol involves scoring of the visibility of normal anatomic structures, and assessing the volume of tissue imaged as a measure of the patient positioning capability of the system. A small study has been conducted to test the viability of evaluating routine mammogram features as a measure of the performance of the imaging system that produced them. The evaluation was planned by radiologists and a physicist at NIH, a statistician from the Office of Surveillance and Biometrics, and OST staff. The results indicate that a reasonable trial (less than one year, a few hundred patients) should be sufficient to demonstrate the performance of the OMS. A draft protocol has been prepared and will be submitted to NIH and FDA human use committees shortly.

Three research projects were started in FY 97 to support the MQSA program. The first project has been completed, and supports the feasibility of assessing noise by providing a selection of noise samples of known characteristics, i.e., a noise step tablet, that observers can use to grade the noise content of images from a system under evaluation. The project was described in the 1997 Annual Report.

The purpose of the second project is to examine the phantom image scoring process used in the American College of Radiology (ACR) Mammography Accreditation Program (MAP) and in the MQSA facility inspection program. Several aspects of the process are being considered. First, the imaging tasks used in the ACR and several other commercially available imaging phantoms are being physically characterized so that their sensitivity to changes in mammography system conditions can be estimated theoretically. This step was completed for the ACR phantom and the CDMAM phantom during FY 98.

Second, the sensitivity of each phantom is being evaluated experimentally. Images of all of the phantoms selected for study were produced using x-ray systems of varying capability. All of the systems were carefully characterized beforehand to allow evaluation of correlations between imaging system characteristics and phantom scores to be derived when the images are read. Scoring protocols for each phantom have been developed, and a set of Visual Basic programs has been prepared to accept readers' responses and place them in a Microsoft Access database for analysis.

OST is also evaluating new approaches to phantom image scoring for both digital and film-screen mammography systems. One such approach is machine reading of phantom images. A program for scoring the ACR phantom is included in the RIT315 diagnostic

radiology software package sold by Radiological Imaging Technology (RIT). RIT has modified the routine so that it saves calculated quality indices for import into a spreadsheet. To test the sensitivity and reliability of the program, it will be applied to 4 sets of 10 nominally identical images, made under conditions producing varying levels of image quality. Variations in the quantitative scores produced by the program within a given set of films will be compared with differences in average values for the sets of films of different image quality. Sample results for the first set of films analyzed (which actually contained 11 films) are shown in **figure 3**.

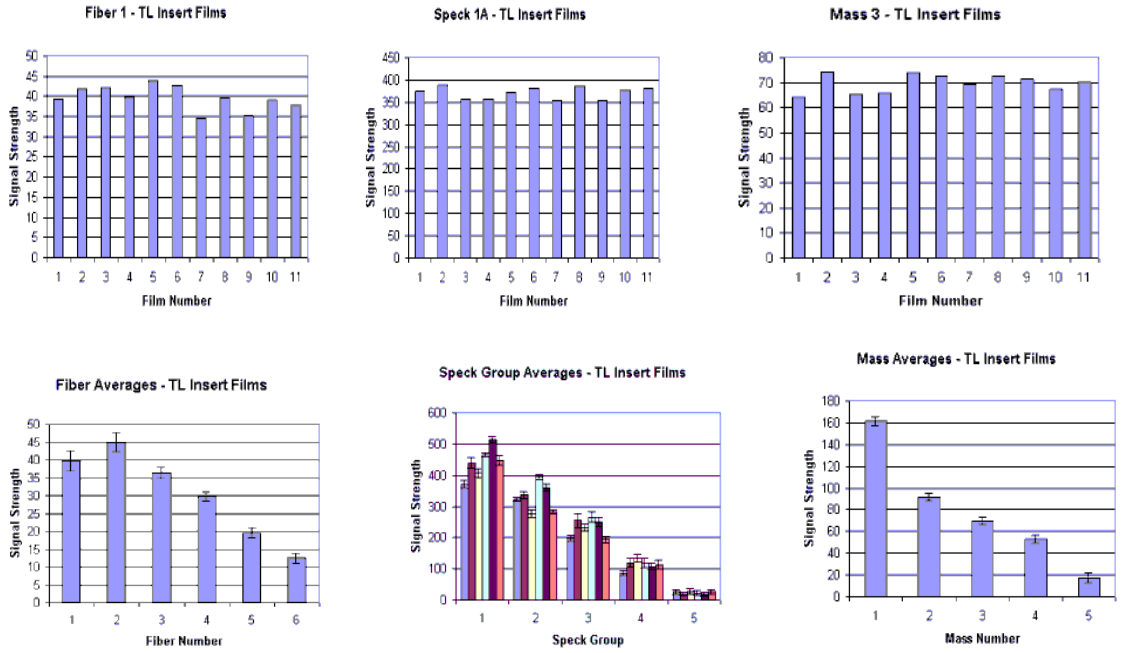

Figure 3. Row 1: Signal strengths (arbitrary scale) from the largest fiber, center speck of largest group, and third mass (each of 11 films per set). Row 2: Average signal strength for each test object (6 fibers, 5 sets of 6 specks, 5 masses). Error bars show one standard deviation, calculated from the 11 measurements.

OST has also used the CAMPI (Computerized Analysis of Mammographic Phantom Images) software developed by Dev Chakraborty, Ph.D. at the University of Pennsylvania. To allow the program to run under Windows NT Workstation on a fast PC platform, a software consulting firm, Image-Smiths was retained to convert the source code from DOS to Windows NT. That work has been completed, and OST scientists are currently checking for consistency of results between the old and new versions of the program. An analysis similar to that described for the RIT package will be done as soon as the final code version is verified.

A third approach applied techniques drawn from the Office's ongoing research on algorithmic observers for image assessment. These observers have the potential of removing human observer bias and lack of precision from the process of evaluating imaging performance. A report on these techniques was presented at the annual SPIE Medical Imaging Conference in San Diego. The algorithmic observer, whose output is expressed as a SNR, is estimated using the high-level language IDL. A comparison of the
output of this algorithmic observer with the results of the CAMPI software has been performed for two sets of images. For this implementation, the observer is most closely described as using the DC-suppressed non-prewhitening matched filter. The results of

this comparison for the center speck in the first three groups of specks in the MQSA/ACR imaging phantom is provided in **figure 4**. As can be seen from the data, the two techniques of estimating the output of this observer (SNR) are quite consistent with each other. As evidenced from the error bars, the estimates of the output of this observer (SNR) are also very precise.

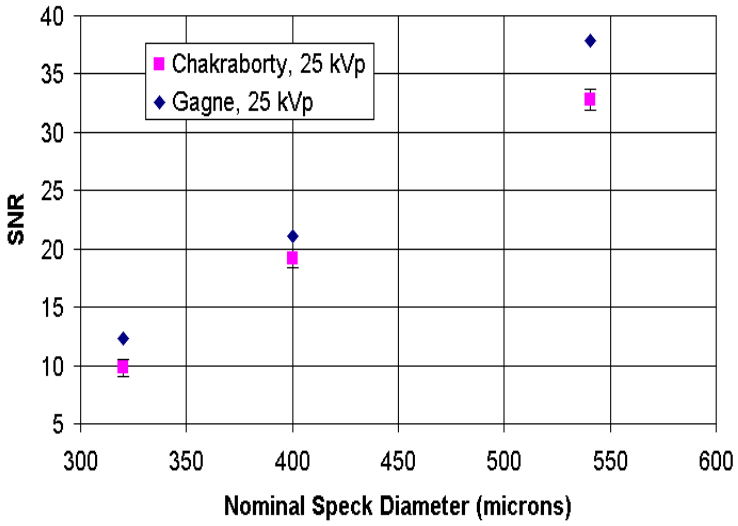

Figure 4. Comparison of SNR values calculated by CAMPI and DC-suppressed, non-prewhitening matched filter (see text for details) for the center speck of the first three speck groups in the ACR phantom.

The third project is intended to provide experimental verification of the exposure-to-dose conversion factors used in the ACR MAP and MQSA inspection procedures. OST is currently using conventional thermoluminescent dosimeters (TLDs) to measure depth dose curves in tissue-equivalent phantoms having a variety of compositions and thicknesses. The phantoms are designed to match the mathematical phantoms used in the Monte Carlo calculations of Wu, Barnes and Tucker that are the basis for the conversion factors to be verified. During FY 98, a graduate student from Georgetown University has evaluated the relative sensitivity of the two TLD types OST scientists are using (TLD100 and copper-doped LiF), determined their energy dependence, and obtained in-phantom measurements for one phantom at two tube voltages with a Mo-anode, Mo-filter x-ray source. Collaborators at NIST have provided the necessary Monte Carlo calculations of the mass energy absorption coefficients for the phantom materials, air, and the TLDs.

Tissue Characterization

Key words: ultrasound, pattern recognition, liver disease, prostate cancer, research

OST, in collaboration with their colleagues from Georgetown University and George Washington University, were awarded funding ($498,382) from the US Army for a research proposal titled: Combining Clinical, Sonographic, and Elastographic Features to Improve the Detection of Prostate Cancer. This will be a 2.5- year effort to apply and evaluate the use of ultrasonic tissue characterization, elastography, and pattern recognition methods OST scientists and collaborators have developed for the detection of

prostate cancer. Preliminary data on excised human prostates have been acquired and analyzed in the past year. OST has supported a Ph.D. graduate student at George Washington University who has investigated methods and underlying mechanisms for ultrasonic characterization of liver disease. This work has greatly enhanced the understanding of the diagnostic potential of this technique. This effort was reported at the SPIE Medical Imaging Conference in San Diego in February 1998 and at the International Symposium on Ultrasonic Imaging and Tissue Characterization held in Arlington, Virginia, in June 1998.

IMMUNOTOXICOLOGY/TOXICOLOGY

Latex-Associated Allergies: Latex Protein Assay Development and Allergen Identification

Key words: latex, allergy, protein measurement, Lowry method, round robin studies, ASTM D5712, ELISA development

Natural latex in medical devices may induce a Type 1 allergy which may be life threatening in individuals highly sensitized to latex proteins. Although awareness of allergy to latex proteins has increased in the last 5 years, the prevalence of latex sensitization is increasing in the general population, as well as in health care providers who use latex gloves in their occupations.

OST scientists are undertaking collaborative research projects that are focused on reducing protein levels on finished latex products and identifying allergenic proteins. One major thrust involves OST participation in the ASTM effort to revise the present ASTM D5712 Modified Lowry method for measurement of soluble latex proteins. Variables such as pH, buffer composition, extraction conditions, and sample clean-up methods in the testing lab were evaluated in order to improve the assay for quantitation of soluble latex proteins. The ongoing round robin studies are addressing these results as it concerns reproducibility, sensitivity, and effects of interfering substances. These questions are answered jointly by the FDA and industry in order to establish a reliable and reproducible protein assay for finished latex products, especially those with a “low protein” claim.

Present laboratory and clinical studies include several *in vitro* and *in vivo* approaches for evaluation of allergenic potential of latex products and identification of latex-sensitized individuals. However, the clinical relevance of various *in vitro* methods has not been established, and the identity of all latex allergens has not been determined yet. The purpose of this project was to evaluate the specificity of the anti-latex IgE antibodies in human sera reacting with latex proteins from various sources. These findings have been correlated with the medical history of test subjects and specific exposure profiles. This study revealed (a) the existence of a number of major allergenic proteins that are present in various latex products, and (b) that the specificity of allergenic response depends on the type of product and the pattern of exposure. While the profile of allergenic proteins varies from product to product, it was assumed that all proteins that may be allergenic are present in nonammoniated raw latex. Therefore, the studies were extended to evaluate the relationship between total protein content vs. allergen content, comparing raw latex extracts with extracts of finished latex products.

Latex protein extracts from three major sources (nonammoniated and ammoniated raw latex and latex products) were evaluated for total protein content by Lowry assay. The level of allergenic proteins was determined *in vitro*, using a pool of human sera and compared to the intensity of skin reactions in sensitized individuals. In clinical studies performed at the Johns Hopkins University, skin testing was performed with these three extracts. The intensity of skin reactions in each patient was the same for all three extracts. These findings indicated that the total protein level may be a reliable measure of the potential allergenicity of latex products. To confirm this finding, OST scientists extended the study to make similar comparisons on the wide range of extracts from finished latex products by three *in vitro* tests. Protein extracts from surgical and examination gloves and other latex products were evaluated for: a) total protein levels by the Lowry assay, b) total antigen level using an ELISA with rabbit anti-latex antiserum, and c) allergenic protein levels using an ELISA with immune human sera.

The comparison of these three methods was intended to reveal which one would be the most suitable predictor of potential allergenicity of latex products. The initial results indicated that the total protein values in the Lowry assay are 10- to 20-fold higher than the total antigen values in ELISA test. A better correlation was observed in the samples with high or very low protein levels.

Complement Activation

Key words: complement activation, cellulose acetate, dialysis, sepharose, protein-A, perfusion, research, standards.

The term *complement* describes a series of serum proteins involved in mediating immune reactions. *Complement activation* is a tightly regulated process which, 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 of the host, particularly against microbial infections, inappropriate activation (such as by implanted or external medical devices which encounter human blood) may result in serious acute or chronic reactions.

Examples of devices whose materials might activate complement include perfusion devices, columns for treating blood externally, indwelling artificial vascular grafts, encapsulated drugs or cells, and vascular shunts. At the request of ODE, OST is conducting research to acquire baseline information needed, in particular, for industry standards concerning testing of materials to be used in blood-contacting devices.

A microassay was developed for assaying whole-complement depletion by solid materials used in the construction of blood-contacting medical devices. This method has been submitted as a draft Standard Practice to the ASTM Committee F-4 on Medical and Surgical Materials and Devices via Subcommittee F04.16 on Biocompatibility. Cellulose acetate fibers and powders used in the manufacture of dialysis membranes were tested using this standard practice. Although cellulose powder potently activated complement (57% reduction from control levels when exposed to an equal volume of serum for 1 hour at 37^{o}C), there was no difference between molecular weight 50,000 versus 30,000. Cellulose acetate fibers were less potent than the precursor powders (only 19% reduction from control levels), though storage time (from dates of manufacture) did not produce significant differences between the fibers (9/96 versus 2/89.) These results suggest that

adverse patient reactions to dialysis by materials could be related to complement activation, which might not be influenced by molecular weight or age of degradation particles.

Sepharose is used to immobilize protein-A in perfusion columns for removing antibodies from patient blood. Both raw sepharose and sepharose-conjugated protein-A were tested for whole complement depletion. Both resulted in a 75% or greater reduction in whole complement activity versus controls. No significant difference was seen between raw sepharose and sepharose-conjugated protein-A, indicating that the majority of the complement activation was due to the matrix, rather than to the attached protein-A. The activation of complement by sepharose was by the alternative pathway (as documented by Bb generation), rather than by the classical pathway (documented by lack of C4d generation). Washing the sepharose with citrate buffers (used in preparing columns for patient blood) resulted in a temporary blockage of complement activation that was rapidly lost upon sequential exposure to additional serum aliquots. These results indicate the potential for complement activation to be a hazard and/or confounding systemic modifier in therapeutic use of antibody-depleting columns.

Endocrine Disruption by Medical Device Materials

Key words: estrogen disruption, uterotrophic assay, heat shock proteins, bisphenol A

CDRH is concerned with the potential for certain medical device materials to mimic or interfere with endogenous hormone actions. Because the hormone estrogen is a potent molecule having profound effects at remarkably low doses, assays are needed to assess the potential for harm from materials that may induce unwanted effects due to interference with normal estrogen homeostasis. OST scientists are collaborating with researchers at the Department of Biology, George Washington University, on projects focused on improving the use of a key biomarker of exposure to estrogenic compounds and determining the characteristics of the estrogenic activity of bisphenol A, a plasticizer found in some medical devices.

OST scientists are modifying and enhancing the traditional assay for estrogenic effects. The traditional assay utilizes the ability of estrogen to cause a hypertrophy of the uterus in ovariectomized or immature female mice. The purpose of these modifications is to provide mechanistic information that will reduce the number of uncertainties in assessing risk from exposure to estrogenic materials. OST scientists are developing an assay that promises to do just that: obtain mechanistic information while examining estrogenic responses in the whole animal. This is accomplished by a side-by-side comparison of the traditional uterotrophic assay and a specific cellular event, the induction of stress proteins, that occurs when estrogen or estrogen-mimicking materials bind to its specific cellular receptor.

Stress, or heat shock, proteins are synthesized rapidly by most cells in response to various chemical and physical stressors, especially heat. This response is thought to serve a cellular protective function. Other functions have been found, and heat shock proteins are called “chaperones” because they appear to associate with other proteins and hold them in proper conformations. This appears to be their function in relation to steroid hormone receptors: they appear to hold the receptor molecule in an open position, so that the receptor can bind to ligand easily. When the ligand binds, the heat shock protein

dissociates; the receptor is free to assume a new shape, one that retains the bound ligand but which also enables the receptor to bind the correct sequence on the genomic DNA, called the hormone responsive element. Thus, OST has tried to identify changes in heat shock proteins as a marker of estrogen receptor binding in tissues from whole animals treated with estrogens.

OST scientists have shown that such changes can be detected in a number of heat shock proteins in the uterus in response to estrogen and that the response is specific to uterine and estrogenic compounds. The effect of exposure time on changes in heat shock proteins was assessed in ovariectomized mice treated with estradiol, the primary estrogen form in the body. Increased relative uterus weight increased linearly between the 4-hour , 8-hour, and 12-hour post-exposure time points, and remained for 1 and 2 days. The histopathology of the uterine lining showed a similar pattern. Changes in the pattern of heat shock protein expression were observed between 6 and 12 hours post-treatment. Thus all three endpoints examined appear at approximately the same time after treatment. This is consistent with the idea that the heat shock protein changes are related specifically to the estradiol effects.

Other steroid and steroid-like compounds were used in order to examine the specificity of the response. The compounds included an androgen, an androgen-receptor antagonist, a progestin, and a partial estrogen. These compounds induced changes in heat shock protein expression, but did not induce uterine swelling. This result demonstrates that the heat shock protein changes are not the result of the stresses to the cells caused by uterine swelling, and the heat shock response may be more sensitive than the uterine response. Compound ICI 182,780, a potent anti-estrogen, had no effect on uterine weights and did not induce changes in heat shock proteins. However, the highest dose of the ICI compound blocked the uterine and heat shock protein effects of co-administered estradiol. Thus heat shock protein induction: 1) is an estrogenic effect independent of uterine swelling; and 2) is a more sensitive indicator of estrogenic effect than is uterine swelling. The histological changes occur in parallel with the uterine swelling effects.

The three endpoints (uterine hypertrophy, histology, and stress protein expression, were used to examine the estrogenic response of the plasticizer bisphenol A. Bisphenol A was determined to be less estrogenic that estradiol (by more than 1000-fold), but caused similar effects. Histological changes in the uterine epithelia were observed at doses 40-fold lower than doses that caused uterine swelling. Although responses were variable, heat shock protein induction was also more sensitive than the uterotrophic response.

Immunological Responses to Silicone Breast Implants

Key words: autoantibodies, silicone breast implants, immunopathology

The breast implant experiments were accomplished in two parts: first to demonstrate immune responses to silicone gel implants in an animal model; and second, to apply the experimental protocols to samples from women with/without breast implants. The objective of these studies was to determine which autoimmune-like symptoms and other symptoms are associated with implanted materials.

OST has developed a rat model to study and understand immune responses to silicone gel and oil used in breast implants. This model included normal rats and a strain of

autoimmune rats, that mimicked clinical conditions found in patients with silicone gel breast implants. Mixtures of silicone gel/oil were injected into the mammary area of female rats. Scientists then measured the levels of autoantibodies to collagen and to nuclear proteins developed over 2 years in response to these mixtures.

Results from the rat model indicate that specific autoantibodies may be induced by certain biomaterials. The immune system recognizes a biomaterial-connective tissue protein association as altered-self or as foreign. OST scientists have demonstrated that medical grade silicone oil can stimulate serum autoantibodies against collagen and against DNA when this oil is injected into mammary tissues of rats. Autoantibody production against connective tissue proteins is an immune response that is consistent with reports from women with silicone breast implants. The results also demonstrated pathological changes in animals that may result from the autoimmune response and that silicone gel can migrate to distant anatomical sites or localize at the implantation site. This work has been presented at The FDA Science Forum, The American Association of Immunology, and The American Association of Biochemistry and Molecular Biology.

The implication from these findings is that leaked oil from a breast implant via leaching or with rupture might provide stimulus for the production of autoantibodies in clinical patients. Therefore, OST scientists evaluated autoantibody levels (in blinded experiments) in serum samples from 150 patients representing four groups: women with silicone implants without connective tissue disease, women with silicone implants with connective tissue disease (CTD), women with connective disease but no implants, and healthy women volunteers. Results from these experiments show in a statistically significant manner that elevated autoantibodies to collagen type I, collagen type II and anti-DNA were detected in serum of patients with CTD, CTD + silicone implants, and silicone implants without CTD.

Using two different assays, autoantibodies to connective tissue proteins (e.g., collagen) and to DNA and intranuclear proteins have been detected in women with silicone breast implants. Historically, there is a strong correlation between anti-nuclear antibodies and clinical symptoms of some autoimmune diseases. OST has documented serum immune responses in these patients with the goal of enhancing the ability to predict the likelihood of immunotoxic symptoms occurring in the presence of implants, including breast prostheses. This work has been presented to the Institute of Medicine.

OST scientists are continuing to investigate these results by correlating this data to the clinical history of the patients. Researchers plan to determine the clinical significance of the data and to study a larger patient population well defined with regard to implants and autoimmune disease symptoms.

Molecular Biomarkers for New Approaches to Safety Assessment: Studies with Mercury
Key words: mercury, stress proteins, kidney, preclinical test method development

An important part of FDA's mission is to facilitate the development, refinement, and validation of more sensitive and predictive preclinical methods in toxicology. One approach is to develop technologies that define molecular biomarkers of exposure and toxicity for ultimate use in preclinical safety evaluation and in risk assessment activities. Prior to acceptance as a standard protocol in preclinical and clinical safety assessment,

these type of approaches must be carefully validated with traditional standards and understood mechanistically for risk assessment applications.

OST investigators are focusing on developing markers at the molecular level because such targets are usually the first responses induced by potentially hazardous materials. Ongoing studies are evaluating the "stress", or heat shock, protein response as a method that will more reliably predict potential adverse effects of device materials.

Mercury is a major constituent of dental amalgam and millions of teeth are filled annually with this material. Mercury, which accumulates in kidney and brain tissues, is one of many proteotoxicants that enhance the synthesis of heat shock proteins (hsps) as part of a cellular defense mechanism. Recently, in a study focused on expression of hsps in kidney in response to mercury injections, OST investigators determined the differential expression of hsps in rat renal cortex and medulla in response to mercuric chloride, a readily soluble form of mercury. The five hsps evaluated were hsp90; two members of the hsp70 family, the inducible hsp72 and the constitutive hsp73; hsp25, and a glucose-regulated protein (grp94). In whole kidney, mercury induced a time- and dose-related accumulation of hsp72 and grp94. Interestingly, hsp72 accumulation was predominantly localized in the cortex and not the medulla, while grp94 accumulated primarily in the medulla but not the cortex. Mercury is toxic primarily to the cells of the proximal tubules located in the cortex. These results demonstrate that hsp expression in rat kidney exhibits regional heterogeneity in response to mercury exposure. The study points out the need to fully understand the expression of particular biomarkers in various cell types and tissues if these new technologies are to be incorporated as surrogates for, or adjuncts to, existing traditional standard methods for safety assessment.

Particulate Effects on Immunologic Function

Key words: particles, cytokines, wear and degradation, macrophages, standards, research

Wear and corrosion of implanted medical devices, such as dental and orthopedic prostheses, may produce particulate debris which may lead to acute and chronic inflammatory responses in the host. In addition, polymeric particles, such as polytetrafluoroethylene (PTFE), may be injected directly into the patients for clinical indications. When particulates are present, the host monocytes/macrophages are activated and they synthesize or secrete mediators of inflammation, and phagocytize particles. In order to understand the mechanisms underlying the host immune response to particulates and device-associated infections, OST scientists have focused their studies on the impact of these particulates on macrophage function. Macrophages play a pivotal role in the body's response to foreign bodies and they also interact with other cellular components in the immune system. OST developed an *in vitro* assay using established murine macrophages. This assay system was incorporated into an ASTM standard on the Biological Responses to Particles (F04.16.01). The inflammatory potential of particles prepared from medical device materials, such as PTFE, titanium oxide, hydroxyapatite (HA), polymethylmethacrylate (PMMA), SiO_2 and fumed silica, polystyrene (PS), $CdCl_2$, CdO, Al_2O_3 , and diamond particle was studied.

In the *in vitro* assay, murine macrophage cells were exposed to particles or chemicals with and without bacterial lipopolysaccharide (LPS), which is a component of bacterial cell walls that mimics bacterial infections. The cells were then evaluated for cytotoxicity,

production of nitric oxide (NO), tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), both inflammatory cytokines. NO is induced by LPS and is critically important in eradicating microorganisms associated with infections, but it can also be harmful by causing tissue injury and vascular collapse. OST studies showed that minute amounts of LPS, which could be associated with a bacterial infection at the site of an implanted device, induced a significant amount of TNF-α, IL-6 and NO production by macrophages.

The *in vitro* studies showed that TNF-α was induced by PTFE, PMMA, TiO_2, HA, SiO_2, both forms of cadmium, and Al_2O_3 particles and by LPS. Polystyrene alone did not stimulate activity. PS in combination with LPS stimulated no activity significantly above the levels in response to LPS alone. Addition of particles to the macrophages did not stimulate NO production. However, addition of LPS to the particles affected the NO production. NO production increased in a dose-response manner with LPS plus PMMA, increased but not in a dose-dependent response with HA, and was inhibited by increasing concentrations of TiO_2. Polystyrene particles in combination with LPS produced minimal and variable differences of NO compared to LPS alone.

The *in vitro* system showed that IL-6 is stimulated by LPS. Neither Al_2O_3 nor PS alone stimulated IL-6 production. IL-6 production was stimulated by Al_2O_3 in combination with LPS, but PS in combination with LPS did not stimulate above the LPS alone level.
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Thus far, the OST studies indicate the following: 1) this *in vitro* system measuring TNF-α, IL-6 and NO responses can detect differences in biological responses to particles; 2) no particle tested by OST thus far has induced NO whereas LPS is a potent stimulator; 3) some particles stimulate TNF-α production and some do not; 4) some particles enhance, some inhibit, and some have no effect on the stimulation of TNF-α and NO by macrophages in response to LPS; and 5) PS particles may serve as a negative control for evaluating the induction of these three biological responses.

Decontaminating Particles Exposed to Bacterial Lipopolysaccharde

Key words: particles, lipopolysaccharide, nitric oxide, macrophage, research

The presence of lipopolysaccharide (LPS) or endotoxin associated with implanted medical devices can stimulate fever in the host. Manufacturers must submit evidence that their sterilized implanted devices are below a given endotoxin level. The most commonly used assay to test for the presence of endotoxin is the Limulus Amebocyte Lysate (LAL) test. OST scientists have observed, using an *in vitro* murine macrophage assay, that LPS stimulates nitric oxide (NO) production. Clean, sterilized medical device particles examined thus far do not stimulate NO production, but certain particles that are contaminated with minute amounts of lipopolysaccharide (LPS, endotoxin) do stimulate NO production. Polymethylmethacrylate (PMMA) particles deliberately contaminated with minute amounts of LPS were assayed for the production of NO in the murine macrophage cell system. Treating particles deliberately contaminated with LPS with 70% ethanol at room temperature or higher for more than 24 hours followed by washing three times with endotoxin-free phosphate buffered saline reduced the level of detection of LPS in the *in vitro* cell system. LPS treated with 70% ethanol also did not stimulate NO production. Both the LAL test and the lack of LPS stimulation of NO production by

murine macrophages show that 70% ethanol can inactivate LPS and may be a method to remove LPS from particles that are being tested for inflammatory potential.

Allograft Heart Valves: The Role of Apoptosis-Mediated Cell Loss

Key words: allograft heart valve, apoptosis, histology

The objective of the study was to determine whether apoptosis of endothelial and connective tissue cells is responsible for the loss of cellularity observed in implanted aortic allograft valves. The method involved retrieving fresh (n=6) and cryopreserved (n=4) aortic allograft valves at 2 days to 20 weeks after implantation in an ovine model. Sections of these valves were studied using histological and electron microscopic methods, nick-end labeling and dual immunostaining for Factor VIII-related antigen and proliferating cell nuclear antigen (PCNA), followed by counterstaining for DNA (DAPI) and laser scanning confocal fluorescence microscopic observation. Results showed that the endothelial cells and cusp connective tissue cells of implanted valvular allografts demonstrated loss of PCNA, (indicative of cessation of mitotic activity), and evidence of apoptosis (nick end labeling). The latter was manifested by nuclear condensation and pyknosis, positive nick-end labeling and formation of intra- and extracellular apoptotic bodies derived from the fragmentation of apoptotic cells. These changes began to develop at 2 days after implantation, peaked at 10-14 days, and became complete by 20 weeks, at which time the valves had the typical acellular morphology of allografts implanted for long periods of time. In conclusion, apoptosis occurs in endothelial cells and cuspal connective tissue cells of implanted allografts and appears to be a cause of their loss of cellularity. This apoptosis may be related to various factors, including immunologic and chemical injury, and hypoxia during valve processing and reperfusion injury at the time of implantation.

INFECTION CONTROL

Attachment to Surfaces Protects Microorganisms From Inactivation by Liquid Disinfectants

Key words: bactericidal compounds, disinfectants, bacterial survival, standard methods.

This study compared the bactericidal activity of seven liquid biocidal compounds and seven popular commercial liquid disinfectants on Pseudomonas aureginosa (P.a.) in suspension and deposited on contaminated surfaces. The active ingredients of commercial products included sodium chlorite, hypochlorite, a mixture of peroxyacetic acid and hydrogen peroxide, phenolics, quaternary ammonium salts, and glutaraldehyde (either at alkaline or at neutral pH). Bacterial survival was measured with a test that is quantitative, rapid, economical, and environmentally friendly. Disinfectants killed a significantly higher number of P.a. in suspension than when the bacteria were attached to stainless steel (screws) or silicone rubber (medical tubing) surfaces. Although most disinfectants reduced the bacterial challenge by 6 to 8 log when P.a. was in suspension, attachment on surfaces resulted generally in 100- to 10,000-fold decrease in killing activity. Furthermore, the activity of some disinfectants was significantly different toward bacteria attached to stainless steel or to silicone rubber. The log killing of P.a. deposited in surfaces under conditions recommended in the product label of commercial

disinfectants was Renalin, 4.5; Exspor, 3.6; Wavicide-01, 3.4; Cidex Plus, 2.9; and cupric ascorbate used as a positive control, 2.8.

These results demonstrated that microbicidal activity of disinfectants and sterilants is 100- to 10,000 fold overestimated by standard methods that challenge microorganisms in suspension. Furthermore, the results of standard methods that evaluate microorganisms deposited on surfaces may be imprecise when the material of the carrier is different from the actual devices to be decontaminated. In conclusion, use of inadequate testing standards and resistance of attached bacteria to commercial disinfectants and sterilants may contribute to a false sense of security that could increase the risk of infections in hospitals, the food industry, and bacteriological warfare.

Microbial Risk Assessment

Key words: infection, microbial risk assessment, dose-response models, Sterility Assurance Levels

The experimental work to assess this from exposure to low doses of microorganisms is described in the section on Infection Control. Because of the technological limits of the experimental studies, mathematical dose-response models are needed to estimate the probability of infection from exposure to very low doses (i.e. one organism) of microorganisms on a device. In FY 98, OST scientists conducted risk assessments of microbial agents on suture materials to provide a scientific basis for the Sterility Assurance Levels (SALs) used by the Center.

Mathematical Model Predicting the Sporicidal Activity of Glutaraldehyde

Key words: glutaraldehyde, microbicidal activity, mathematical models

Glutaraldehyde is the active ingredient most frequently used in commercial products employed in liquid sterilization of medical devices. Investigators in OST have experimentally shown that the microbicidal activity of glutaraldehyde is affected by concentration (C), temperature (T), pH, ionic strength (μ), aging (a), and organic matter or serum (s). A mathematical kinetic model was developed with an exponential equation (describing the effects of C, T, pH, μ, a, and s) that predicted the sporicidal activity (on *Bacillus subtilis globigii* spores) of glutaraldehyde within a log of its experimental activity for a broad range of conditions. The model predicted the effectiveness of glutaraldehyde-based commercial products, particularly when limited data is available. This study demonstrated that performance standards for liquid sterilants and disinfectants could be established mathematically. Furthermore, practical situations that result in inefficient disinfection could be predicted, and therefore prevented.

Radioactive Versus Luminescent Detection of an Arenavirus After PCR Amplification

Key words: Arenavirus, Junin virus, ^{32}P radioactivity, luminescence

OST molecular biologists, together with a visiting scientist from Buenos Aires, Argentina, compared radioactive (^{32}P) versus nonradioactive (luminescence) detection of Junin virus, a human RNA-containing Arenavirus, after amplification by the polymerase

chain reaction procedure (PCR). For reasons associated with safety and possible environmental contamination, the OST laboratory is planning to convert from radioactive to nonradioactive procedures, and it was necessary first to compare these different types of detection. The RNA of Junin virus was isolated, reverse-transcribed enzymatically, and a resulting "cDNA" copy was amplified by PCR. The amplified DNA was isolated by gel electrophoresis and blotted onto DNA transfer membranes. A Junin virus-specific DNA probe was then labeled with ^{32}P, or with a suitable non-radioactive compound (digoxigenin), and hybridized in solution to the amplified viral cDNA. Standard immunology and radioactivity detection techniques were used to quantify the results. The procedure involving radioactive labeling required less manipulation and was cheaper. However, by proper selection of experimental conditions, luminescence could be made more sensitive than ^{32}P labeling. Further justification for conducting this project is the fact that Arenaviruses cause fatal hemorrhagic fever in humans, and rapid diagnosis of arenavirus infection is an important human health issue.

Transmissible Spongiform Encephalopathies (TSEs) and FDA-Regulated Products

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

As a key member of the FDA InterCenter TSE Working Group and Chair of the CDRH TSE Working Group, the Center Coordinator for Biotechnology has demonstrated leadership and consistent and productive outstanding scientific expertise and efforts in spearheading Agency initiatives. These initiatives are to resolve numerous cross-cutting scientific and regulatory issues regarding TSEs that impact FDA-regulated products with broad implications for public health. Following reports of a variant form of Creutzfeldt-Jakob Disease (vCJD) in humans in Great Britain in 1996, attention immediately focused on a possible link of this human TSE disease to bovine spongiform encephalopathy (BSE), of high incidence in the cattle of Great Britain, and upon the many products using bovine-derived materials.

The FDA TSE Working Group was charged with assessing the impact of BSE and the new vCJD on FDA-regulated products and the actions that could be taken to protect public health and to alert industry to appropriate safeguards measures. These FDA scientists, working with each other across FDA Centers and with their sister agencies, had begun to share scientific expertise about BSE and other TSEs in animals and humans a decade before when the cattle disease BSE in Britain became the epidemic known as "mad cow disease." The goal was to prevent a possible occurrence of BSE within the United States. Cross-species transmission was a concern because it was thought that BSE may have resulted from exposure of cattle to a TSE in sheep (scrapie) via rendered sheep tissues in cattle feed. Since the 1996 charge, the Working Group took a number of steps to productively address the significant scientific and regulatory issues of TSE for the agency. These included letters to the industry, recommendations and guidance, and organization of meetings of the FDA TSE Advisory Committee. These steps were taken to allow for public input to proposed Agency actions and to increase the level of confidence that FDA-regulated products are free of potentially infectious material.

The work of the last 2 years culminated in the Workshop on TSE Risks, held June 8-9, 1998, an international conference sponsored by the Joint Institute of Food Safety and Applied Nutrition (JIFSAN). JIFSAN is a joint endeavor of FDA and the University of

Maryland. As co-chair of the Organizing Committee, the Center Coordinator for Biotechnology was instrumental in developing a focused agenda and a productive meeting, which included industry, consumers, academia, the European Community's Scientific Steering Committee, and other governments and international organizations. The workshop was unique in its attempt to develop a systematic approach for addressing TSE risks, and it set the stage for an ongoing, scientific dialogue among those who advise, world-wide, those officials responsible for difficult regulatory decisions. A major workshop product is an outline of critical elements to consider in addressing TSE risk assessment questions.

The final stage of this product is a generic framework of practical guiding principles for TSE risk assessment related to raw material sourcing, material processing, and end-product use. A workshop summary will be published in the January 1998 issue of the journal, *Emerging Infectious Diseases*, and the workshop transcript, summary, and stage one of the framework document is posted on the JIFSAN web site. Another workshop product is the TSE Risk Web site, an information tool that will allow individuals around the world to quickly access and relate specific and detailed TSE risk-related information applicable to a particular situation. In addition to the JIFSAN Workshop, the Center Coordinator for Biotechnology presented FDA's proposed course of action to address the potential TSE risks associated with human dura mater allografts to the FDA TSE Advisory Committee at its April 1998 meeting. The Committee agreed with FDA's proposed course of action, and the Draft Guidance to Dura Providers (one element of this action) has been completed. In addition, the following guidance has also been completed and issued: Guidance for FDA Reviewers and Industry: Medical Devices Containing Materials Derived from Animal Sources (Except for *In Vitro* Diagnostic Devices). Participation in several national and international forums, such as the American Occupational Health Conference has enabled the education and communication of Agency actions on TSEs and FDA-regulated products to the greater scientific community.

Device Reuse Project

Key words: Reuse, cleaning, disinfection, catheter, compliance testing

Effect of cleaning solutions on materials

The effect of various cleaning solutions on materials properties was tested for a range of generic polymeric materials: latex, nylon 6/6, 2 polyetherurethanes: pellethane 2363-75D and 2363-80A, and silicone. Standard ASTM D412 tensile specimens (size "D") were cut from these materials and exposed to various solution combinations, including: 1:10 dilution of Clorox, detergents, and blood. The effect of ethylene oxide (ETO) sterilization on these materials was also evaluated. Specimens were tested in tension according to ASTM D412 & D638. Parameters measured included strength (yield and/or ultimate) and elongation. The data demonstrated that the effect of cleaning solutions on polymeric materials is material-specific, not generic.

The effects of Clorox on the corrosion of reusable surgical instruments was also examined due to concerns about AISI 303 stainless steel. Type 303 is known as a free machining high sulfur alloy. Due to the formation of manganese sulfides, it has a higher corrosion rate than other 300 series stainless steels. Potential monitoring of type 303

specimens with a teflon crevice corrosion collar showed severe crevice corrosion in the presence of dilute solutions: 1:10, 1:50 or 1:100 of Clorox (5.25% sodium hypochlorite).

Analysis of used PTCA catheters (percutaneous transluminal coronary angioplasty)
A retrieval program was set up with Walter Reed Army Hospital in August 1997, where PTCA's were collected which had been used in a single patient. They were placed in a bag of water and brought to the laboratory where they were disinfected. The protocol for these used PTCA catheters was to clean, inspect for damage (kinks, etc.), compliance test, and wash and dry the balloon. To date, over 250 have been retrieved and tested.

A cleaning protocol developed in FY 97 was used. Clorox was added (to make 10%) to the bag for 1 hour to clean and disinfect (for blood-borne viruses). The guide wire lumen was flushed of blood with 10% Clorox, and the catheter placed back in the bag and left for 30 minutes. The outside of the catheter was then rinsed in enzyme detergent (Gain), the guide wire lumen flushed with detergent, the outside and the lumen flushed well with water, and the balloon and lumen flushed with water at least three times and then stored for later testing.

The data are still being collected and analyzed for the various types of catheters obtained. Ease of removing blood and debris, precipitation of contrast dye in the balloon and balloon channel, balloon compliance compared to specifications, and balloon rupture are all being evaluated. The results of this research will be examined by management to evaluate issues connected with reuse of single-use devices.

Validation Studies of Virus-Transport Modeling

Key words: computational fluid dynamics, barrier devices, modeling, virus

Synthetic barriers such as gloves, condoms, masks, gowns, and instrument sheaths are critical elements of the worldwide disease prevention strategy. Tests of the effectiveness of barriers to virus transmission are often performed under circumstances which do not reflect actual use conditions. For example, static conditions are employed or laboratory-safe viruses or virus surrogates are used. In order to extend laboratory results to more general conditions, as well as to analyze the physical mechanisms governing virus motion within barrier passageways, a mathematical model for simulating virus transport through synthetic barriers was recently developed.

The mathematical model is based upon the perfect-sink boundary condition, in which viruses contacting the pore wall are assumed to be irreversibly adsorbed. Calculations derived from the model were compared to the results of calibration experiments using bacterial viruses and latex membranes. These comparisons revealed, under certain conditions, a much higher rate of virus transmission than predicted. These discrepancies could reasonably be attributed to reversibility – desorption of viruses back into suspension - or to saturation of potential virus adsorption sites.

A new set of virus-transport experiments resulted from a desire to test the extent to which reversibility and saturation limit the applicability of the perfect-sink model of virus adsorption to synthetic barriers. Each experiment incorporated the bacterial virus PRD1 suspended in saline, with the suspension flowing through a channel comprised of two sheets of latex separated by a small distance (about 100 microns).

The first experiment involved the measurement of virus transmission through the channel as a function of time. In the presence of saturation or reversibility, the transmission through the channel should increase with time, as adsorption sites are no longer available (saturation) or viruses bound early in the experiment desorb back into suspension (reversibility). If equilibrium is established and adsorption equals desorption, then a 100% transmission rate results. The second experiment involved measuring virus transmission as a function of virus titer input into the channel. Saturation and reversibility should be manifested earlier in the experiment for higher virus concentrations. Titers spanning four orders of magnitude (from 1000 to 10 million viruses/ml) were included in the protocol. The final experiment involved two rinses of the channel following transmission experiments to see whether bound viruses could be eluted by pure saline (first rinse) or by a nonionic surfactant (second rinse).

Results of the first experiment showed that the virus transmission through the channel was very steady, even for observation times far in excess of the original calibration experiments motivating the reversibility and saturation hypotheses. For the second experiment, no difference in transmission was found between the input virus concentrations – the same fraction of viruses was adsorbed for each titer. In the final experiment, rinses of the channel with pure saline eluted essentially no viruses, while the rinse with the surfactant eluted all viruses that were "missing" input into the channel but not exiting during the transmission phase. This final experiment showed that PRD1 virus is essentially irreversibly bound to latex in the presence of saline. The nonionic force holding the virus to the latex surface is weakened enough by the surfactant to allow the virus to detach. Thus, the model of a surface able to irreversibly adsorb large numbers of viruses without a change in adsorption rate, i.e., the perfect-sink model, appears to hold well for conditions under which synthetic barriers are tested, namely with bacterial viruses suspended in a saline solution.

The underprediction of the transmission rates by the model during the original calibration experiments was then re-examined as a sensitivity of the model to variations in the channel geometry. A rectangular geometry was used in the model similar to the experimental design of two latex sheets separated by spacers. However, since the sheets were separated by a very small gap, details of the channel geometry were impossible to ascertain. The latex sheets could well have "protruded" into the rectangular volume in various locations. Calculations using nonrectangular geometries showed that for highly adsorbing viruses such as PRD1, the transmission rate is highly sensitive to details of the pore geometry, particularly the minimum gap in the channel. Consequently, an additional set of calibration experiments was performed using larger channel gaps and light clamping, ensuring a more rectangular geometry. To achieve a long enough residence time in the channel (allowing viruses to diffuse across the large distance and interact with the latex before they exited the channel), the channel was tilted to a near-horizontal position, thereby effectively reducing the gravitational force. With the more controlled geometry, the agreement between measured transmission rates and the model predictions was much better.

This project demonstrated that the perfect-sink approximation is valid for modeling virus adsorption to synthetic barriers under conditions relevant to barrier testing. It was also observed, however, that for highly adsorbing viruses, details of the pore geometry must be known in order to accurately simulate the virus transport.

Validation of a Corona Discharge Technique to Test Male Latex Condoms for Defects

Key words: latex, condoms, holes, electrical discharge

The Food and Drug Administration uses a water leak test to examine manufactured lots of latex condoms before allowing them to be sold. This test can reliably detect holes with diameters as small as 15 microns. More sensitive albeit much more complicated and time-consuming tests have been devised by the FDA. Two of these tests determine whether 110-nm fluorescent beads or a 27-nm bacteriophage are transferred from the interior to the exterior of a condom. These methods are capable of detecting holes down to diameters of approximately 4 microns and 2 microns, respectively. However, none of them can be used online, during manufacture. To date, no quick or simple technique has been available to test condoms to the above sensitivities.

As part of FDA's continuing effort to evaluate potentially better methods for assuring the adequacy of medical devices, a product that uses an electric discharge to detect small holes in the condom material was purchased and a study completed which evaluated its capabilities. This product utilizes an aluminum mandrel, shaped such that the latex condom to be tested must fit snugly over it. The mandrel sits in open atmosphere. A series of 16 electrodes are positioned in a plane and along the length of the condom to be tested. Each electrode is maintained at a high positive voltage relative to the aluminum mandrel. This voltage is pulsed, with a frequency in the kilohertz range. Surrounding each electrode is a tube through which is delivered nitrogen cover gas. The distance of the electrodes to the mandrel, the voltage, the frequency, and the rate of flow of the nitrogen are all adjustable. A high impedance resistor is placed in series with each sensor.

If the voltage is adjusted correctly, very little, if any, current flows unless a hole exists in the latex condom covering the mandrel, and then a corona discharge completes the electrical circuit. When this occurs, the change in current in any of the 16 sensor circuits can be analyzed by a data acquisition system, or noted by a light emitting diode (LED), located on each of the 16 sensors. The electrode geometry, voltage, frequency, resistor impedance, electrode distance and rate of flow and type of cover gas all affect the nature and duration of the discharge and hence the current. The mandrel can be rotated, such that the sensor bank can virtually map out the entire condom surface, including the tip.

Holes of known size, utilizing an excimer laser, were drilled in nonlubricated, reservoir-tipped latex condoms. Hole sizes ranged from approximately 1 to 30 microns in diameter and locations ranged along the shaft and at the closed reservoir tip of the condom. Furthermore, as controls, condoms with no holes were tested. Testers who had no knowledge as to the actual hole sizes or locations examined all condoms. The lighting of the LED's on the sensors indicated detection, and the particular sensor(s) lit were noted.

Out of 43 condoms with holes, the device correctly identified 42. Out of 22 condoms without holes, 21 were correctly identified as being intact. One 2-micron hole, near the open end of a condom, was undetected. One condom without a hole was incorrectly identified as having a hole. These percentages compare favorably with the other tests described above.

Our validation study's conclusion is that this device is a useful laboratory tool, with sensitivity at least as good as and ease of use better than anything else available. Indeed, the sensitivity might be much greater than our test would show. Also, considering its capabilities and characteristics it seems probable that this method has potential as an on-line test in a manufacturing setting.

Virus Impermeability of Differently Formulated Natural Rubber Latex Films and Gloves

Key words: latex, natural rubber, virus, permeability

The issue is still raised about the permeability of latex gloves and condoms to virus passage, despite published data indicating that most such products are effective barriers to even small viruses. The threat of AIDS has led to manifold increase in the use of latex gloves and concern about their effectiveness. A visiting scientist from the Rubber Research Institute of Malaysia participated in a collaborative study in an OST lab to develop a test of permeability that might differentiate between permeation (passage through the basic, nondefective material) and penetration (passage through a defect in the material, e.g., a hole). The study tested the porosity of gloves and latex films prepared by certain formulations that might affect the integrity of the film. Films were prepared in Malaysia having different sources of high-ammoniated latex concentrate, different levels of non-rubber constituents, different modulus, either post- or prevulcanisation, or different leaching processes. In addition, film samples and gloves were artificially aged at 70 ^{o}C.

To optimize the test, the films were stretched to their maxima (nine-fold in area) and subjected to high titer of the challenge virus, ϕX174. The three-phase test could determine where any virus passage occurred and how much. Although this three-phase test was conducted at low pressure, it could detect open holes as small as 2 microns in unstretched films and tears made with a very thin needle in stretched films. Since stretching the material would stretch a hole (9X or more) and produce a much thinner film, it is expected that even smaller holes should be detectable. All the latex films representing a wide range of formulations and ages were effective barriers to transmission of the small virus. Thus, permeation through quite thin, stretched samples with this very sensitive test was not found. This is interpreted to mean that there are few, if any, pores or holes through unstretched latex films large enough to allow virus passage in a reasonable time.

This is consistent with previous findings that latex condoms are effective barriers over longer test periods at much higher pressures and that intact latex gloves are also effective barriers. It is also consistent with the recent demonstration that ASTM Standard Test Method F1671 could detect laser-drilled holes in condom latex down to about 1 micron, but none in control samples without intentional defects. Similarly, latex condoms tested over 1-16 days allowed no virus passage by permeation and diffusion. Thus, this combined evidence indicates that the holes reported in the scientific literature are not common to laboratory-prepared latex samples nor to marketed latex condoms or gloves, but must be considered as occasional defects subject to effective quality control procedures.

Characterization of ASTM F1671, a Barrier Integrity Test for Surgical Gown Material

Key words: barrier material, virus, standard, ASTM

In a collaborative study with ODE, a modified version of ASTM Test Method F1671 (Test Method for Resistance of Materials Used in Protective Clothing to Penetration by Blood-Borne Pathogens Using Phi-X174 Bacteriophage Penetration as a Test System) was characterized using latex pieces with laser-drilled holes of documented diameter. Virus penetration was detected for all holes with diameters above 1.0 micron. No virus passage was found in control samples with no intentional defects. The quantitative results were in good agreement with calculated fluid flow through a cylinder (Poiseuille equation) for holes above 2 microns. Thus, this test method can detect a single 1-micron hole, but can only detect smaller holes if there are many of them. For example, at least 10,000 holes of 0.1 micron diameter would be needed for detection. In addition, an argument based on capillary flow through small pores suggests that the final phase of the test, a 54-minute period at no pressure, serves no useful purpose and should be eliminated from the test protocol.

Condom Holes Important for High Titer, High Infectivity Viruses

Key words: condoms, risk, holes, breaks, virus infectivity

During an analysis of the implications of laboratory tests of condom integrity, it was determined that breaks during use were much more important than holes when considering risk from infection of low titer, low infectivity viruses such as HIV. For such viruses, relatively large exposures to semen (0.1-1.0 mL) are necessary for disease transmission. For high titer, high infectivity viruses, smaller volumes of semen exposure can have significant risk. In such cases, the presence of holes can be as important as breaks. That is, the relative importance of breaks and holes is related to the volume of semen that constitutes an “infectious dose.” Extrapolating from laboratory data for virus passage through latex condoms, the percentage of condoms that allow an “infectious dose” of semen to pass was determined, i.e., the percentage that allow 0.1 mL to pass, or 0.01 mL, etc. This approach demonstrated that where relatively large semen passage is necessary for disease transmission (i.e., 0.1 or 1.0 mL), only breakage of condoms is important, as mentioned above. However, as smaller volumes are considered, holes contribute more. In fact, holes detectable by the water leak test contribute to the risk for semen passage of 0.01 mL. Holes not detectable by the water leak test become important for semen passage less than 0.000,01 mL. At this level of semen passage, holes (combined water leak detectable and undetectable) become as important as breaks.

Salinity Affects Virus Passage Through Track-etch Filters

Key words: track-etch membrane, sieve filter, virus, salinity, adsorption

This project resulted from a finding that track-etch filters, used for sterilizing medically-important fluids such as physiological saline by removing contaminating viruses and cells, sometimes did not allow passage of viruses known to be smaller than the pore size of the filter. A mentorship student from Thomas Jefferson High School for Science and Technology, Alexandria, Virginia, developed the project protocols and the initial data. Special filters were generously provided by Corning, Inc., Acton, Massachusetts. Passage of viruses (X174 or PRD1, diameters of 27 and 65 nm, respectively) through certain commercially available or specially-coated 200-nm (rated pore size) track-etch membranes was restricted with increased salinity (over the range 0.8 to 160 mM [Na^+]). This demonstrated that track-etch filters are not just simple sieves that indiscriminately pass particles smaller than the pore size. The results at 160 mM verified the earlier finding that certain viruses do not pass through track-etch membranes with larger pore sizes. A nonionic surfactant (0.1% Tween 80) minimized or even prevented the virus adsorption, implying that nonionic interactions are responsible for virus adsorption. This result also indicates that this surfactant, and perhaps others, can be used to avoid misleading results when such filters are used for virus-size determination. Previously it was believed that increased ion concentration was necessary for virus adsorption. These data indicate that the role of increased ion concentration is that of screening the negative electrostatic charges that prevent virus adsorption (by nonionic interactions) at lower salinity. These results demonstrate that an understanding of virus/membrane interactions is valuable in predicting filter membrane performance.

Sterility Assurance Levels

Key words: infection, sutures, staphylococcus, SAL, standards, tech support

OST scientists completed a project to determine the adequacy of sterility assurance levels (SAL). A manuscript describing the study has been accepted for publication by Journal of Biomedical Materials Research. The data are being used for a risk assessment analysis and an AAMI standard. The specific scientific question asked was how many organisms does it take to cause an infection, or what is the infection rate with low numbers of organisms on an implanted device? The data will be used to determine the impact on infection risk if the currently required SAL (the probability that one device in a million might be nonsterile) were changed to a probability as low as 1 in 1,000. The study demonstrated that the infection risk in the mouse model when less than 10 organisms were present was approximately 6%. However, for one type of suture it was 15%. The data are being used by AAMI and by CDRH/ODE for consideration of SALs for materials that undergo degradation with the more intensive sterilization procedures required for a SAL of 1 in 1 million.

Health Issues Related to Reuse of Single-Use Devices

Key words: cleaning, reuse, percutaneous transluminal coronary angioplasty (PTCA), disinfection

Some medical devices are designated as reusable and are cleaned and sterilized for use in additional procedures. Some devices are designated as single use and are to be discarded after one use. However, in the attempt to reduce health care costs, some health care facilities are attempting to reuse single use devices. OST scientists are conducting experiments to optimize cleaning procedures for reused devices, whether it be a multiple-use or a single-use device. A 96-well polystyrene plate format was used as a surrogate medical device because this provided a design that could not be scrubbed clean and provided the opportunity to collect optical density measurement data in order to objectively assess procedure efficacy. Biological material, including bacteria, protein, mammalian cells, and blood, was allowed to adhere to the plates. Plates were then cleaned and tested for cleanliness using dyes and optical density measurements. Crystal violet was used to stain the bacteria and Bradford reagent was used to detect the presence of protein and cells. Several protocols were followed, and cleaning was successful with sodium hypochlorite (bleach). The use of detergent with enzymes following a bleach soak was advantageous in removing final traces of biological material and in removing the bleach. This is our recommended cleaning protocol. This provides low-level disinfection, making the device safe for handling by the cleaning personnel for the detergent treatments and provides sufficient cleaning for subsequent sterilization.

Subsequent experiments were designed to evaluate the effects of cleaning and re-sterilization on single-use PTCA balloon catheters. These were obtained from Walter Reed Army Medical Center after use in a single patient. The devices were soaked in bleach before being handled. The wire guide lumen was flushed free of blood using bleach and then left to soak in the bleach. The catheters were rinsed with detergent with enzymes, followed by a wash with water. The balloons were flushed of the radiopaque dye using water. The devices were then tested for balloon compliance. Testing with crystal violet stain and with Bradford reagent indicated that the catheters were successfully cleaned.

A simulated reuse protocol was also developed involving immersion of the catheter in a bag of blood, filling the wire guide lumen with blood, and inflating the balloon to 6 psi with water. This was left for 2-4 hours with occasional agitation of the blood in the bag. The catheters were then cleaned according to the established protocol, ethylene oxide gas sterilized, the balloon compliance tested, and the process repeated. Different catheter types (from several manufacturers) have been obtained and tested. Some of the catheters had balloon compliance outside of the recommended specifications after a single use or after simulated reuse.

LASERS

Infrared Fibers for Laser Delivery

Key words: optical fibers, infrared radiation, technical support

The use of infrared lasers for treatments such as therapy for wound healing and other surgical procedures is likely to increase. The use of lasers for these clinical procedures frequently requires the use of optical fibers to transmit the laser radiation to the desired location for treatment. While such fiber optic bundles are common in the visible spectral

region, fibers that transmit infrared radiation are of inferior quality at this time. Furthermore, many of the materials currently used in infrared fibers are toxic to humans.

Under a contract with the Office of Naval Research and a similar contract with the Air Force Office of Scientific Research, OST scientists are investigating the performance of new types of infrared fibers and waveguides for medical use. Several collaborative projects are underway with outside scientific laboratories.

One area of study focuses on the use of low-level laser treatments to reduce healing time for certain skin conditions. In FY 98, tests on several Spraque-Dawley rats revealed accelerated wound healing when irradiated with low level laser light. This work was carried out collaboratively with scientists at USUHS and will be continued with normal and diabetic sand rats to evaluate the impact that laser therapy might have on human diabetic wounds.

In FY 98, OST scientists developed a method of delivering and receiving energy to tissue that should be much safer than direct beam methods. The essence of the device is in a specially prepared tip. When connected to a laser, the fiber containing the special tip simply directs the laser energy to a beam dump prior to contact with tissue. However, when tissue is contacted, energy flows from the fiber to tissue. In addition, for as long as contact with the tissue is made, the fiber transmits information on the ablation process back to the researcher so that shock waves, bubble formation and collapse, tissue blow-off and temperature can be monitored.

In addition, studies are continuing with newer fibers which reduce energy transmission losses due to fiber bending. Tests on new chalcogenide fibers obtained from the Naval Research Laboratory have shown almost no transmission losses even when bent to a radius of about 2 centimeters. These fibers can have the special tips installed to collect and deliver laser energy throughout the mid-infrared spectral region.

Cyanide Production from Laser Ablation of Uric Acid Stones

Key words: surgical laser fibers, minimally invasive surgery, uric acid stones

Pulsed laser lithotripsy, using a dye laser operating in the visible at 504 nm and a pulse width of 1 microsecond, has been approved for the noninvasive fragmentation of stones, or calculi, located in the bladder or ureter. This minimally invasive procedure uses fiber optics to deliver the laser energy to the targeted stone. These pulsed lasers have also been used to fragment calculi in the common bile duct, during retrograde nephroscopy, and percutaneous nephrolithotomy. The green pulse is absorbed in the calculi and creates a rapidly expanding plasma, which results in a photo-acoustically driven shockwave to shatter the stone. This green wavelength is not readily absorbed in the ureter wall, and hence its use provides some protection from adjacent tissue damage. However, stone recoil occurs following pulsed dye laser absorption so that fragmentation must be done carefully so as not to lodge the stone in the duct wall. Larger stones require more pulses than smaller stones for fragmentation and removal.

Recently, the Ho:YAG pulsed solid state laser operating at the infrared wavelength of 2100 nm with a pulse duration of 250 microseconds has also been approved for laser lithotripsy of urinary calculi. Because of the difference in wavelength and pulse duration,

the stone is primarily drilled and not fractured. Unlike the pulsed dye laser, fragmentation is achieved by drilling a number of holes in the stone, which ultimately results in stone fragmentation. Additionally, the Ho:YAG's laser pulse is readily absorbed in the ureter wall. In order to help prevent adjacent tissue wall damage, the pulse energy should be limited to 1 Joule or less.

The pulsed Ho:YAG laser radiation is absorbed in the stone creating a photo-thermal event. The absorption of the Ho:YAG pulse increases the stone temperature but doesn't create a plasma. It has been shown *in vitro* that this photo-thermal event is responsible for the production of cyanide when the Ho:YAG laser is used to assist in the removal of uric acid based stones. It is well known that cyanide is produced from heated uric acid. To date, this event has not been observed to produce an adverse event in treated patients. This is probably due to the fact that the ablation site is continually flushed with liquid during the procedure.

However, in response to this Ho:YAG laser-uric acid calculi-cyanide production, CDRH formed an ad hoc committee to address this potential safety issue. The committee has asked the Office of Science and Technology to provided additional laboratory data to assist in the hazard analysis. In response, scientists in OST have designed an experiment to attempt to answer two scientific questions: 1) Does the amount of cyanide produced by the absorption of the Ho:YAG laser pulse and a uric acid stone scale with the total amount of laser energy, and 2) Does the cyanide production rate depend upon the size (diameter) of the delivery fiber? Answers to these questions will help to determine what the potential risks are for this particular indication, and whether cyanide production can potentially harm a patient.

Laser Transmyocardial Revascularization and Percutaneous Myocardial Revascularization

Key words: surgical laser fibers, cardiovascular surgery

Transmyocardial laser revascularization (TMR) is a therapeutic surgical procedure that has been shown to provide relief from chronic angina. One company has recently received FDA approval for its high-powered CO_2 laser for this indication. Another company has received panel approval and is awaiting FDA approval for its Ho:YAG laser. Both companies are continuing to follow their patients via postmarket surveillance. Typically, TMR provides a therapy for patients with ischemic heart disease that is not amenable to percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass grafting (CABG) and is unresponsive to medical therapy.

TMR involves using the laser beam to produce a series of channels in the ventricular wall of the heart, ablating from the epicardium to the endocardium. This is commonly done in an open surgical procedure, although it may also be done in a minimally invasive manner. It is always performed upon a beating heart without the assistance of a heart-lung machine (assuming CABG is not performed). TMR may require only a 4-inch incision on the left side of the chest, avoiding the thoracotomy needed during CABG.

Percutaneous myocardial revascularization (PMR) is a minimally invasive surgical procedure. It is similar to TMR except the laser ablated channels do not completely penetrate the myocardium, and the laser radiation is applied at the endocardium not the

pericardium. This procedure is facilitated by an optical fiber which delivers the laser energy percutaneously. The high-powered CO_2 laser is not suitable for PMR, as an appropriate flexible fiber optic delivery systems is unavailable for this type of laser. The Ho:YAG and the XeCl excimer laser are undergoing clinical trials for PMR.

Recovering patients who have undergone TMR have decreased in angina class, decreased in subsequent hospital admissions, and improved in myocardial perfusion (30-month data). The actual mechanism responsible for this improvement has not been identified. Initially it was thought that the channels remained patent and supplied blood to ischemic areas of the myocardium. However, most autopsies of human hearts which have undergone the procedure showed that the TMR channels do not remain patent. This issue remains controversial. Angiogenesis has been found as a result of the channel surgery. It may be that high cytokinetic concentrations, which are typical of thermal damage, are responsible for this angiogenesis. Also, macrophage and monocytes produce a variety of angiogenic growth factors. Alternatively, it has been shown in the canine model that the production of the channels destroys nerves in the myocardium. This laser-induced inhibition of pain allows exercise-induced neovascularization to occur. It may be that all of these factors: angiogenesis, pain inhibition, and a few patent channels play a roll in the success of TMR. For those trials where patients knew that they received TMR, the placebo effect may also play a role in the treatment's success.

The FY 98, scientists in OST began designing an experiment to investigate the optical absorption and ablation rates for the two lasers (Ho:YAG and XeCl) used for PMR. During PMR it is critical that the partial channel doesn't accidentally penetrate through the myocardium. Currently there are no published absorption coefficients for the 2100-nm wavelength (Ho:YAG) and the 308-nm wavelength (XeCl) in myocardial tissue (human or animal). Knowledge of the absorption coefficient and other variables allows for the calculation of theoretical ablation rates for these laser sources. In addition, measurements in phantom myocardium (swine, canine) will help to verify the theoretical ablation rates and can be compared to those obtained in animal studies of TMR and PMR.

MATERIAL DEGRADATION

Risk Assessment Methods Development

Key words: risk assessment, route-to-route extrapolation, sensitive subpopulations

Developing standards and guidelines for the derivation of allowable limits for chemical compounds in medical device materials requires new risk assessment approaches to be created and validated. Several novel approaches have been developed by OST staff in FY 98 to permit the implementation of the risk assessment-based approach for systemic toxicity assessment described above.

CDRH staff are often asked to make regulatory decisions based on little available data. For example, toxicological data are often unavailable from clinically relevant routes of exposure to derive protective health-based exposure limits (HBELs) for compounds released from medical device materials. As a result, the need exist to develop tools that will allow Center staff to extrapolate toxicological results obtained following administration via one route of exposure to those expected from another route. Although route-to-route extrapolation can be conducted with the use of physiologically based pharmacokinetic (PBPK) models, the

software and expertise to run the models is not universally available. In lieu of a model- and data-intensive approach to route-to-route extrapolation, OST staff in FY 98 have derived simple, default conversion factors that will enable a risk assessor to estimate the toxicological or pharmacological potency of a compound for one route of exposure based on data from another route.

In FY 98, OST researchers have also examined whether sick or injured patients, as a sensitive subpopulation, are adequately protected by the current approach used to derive HBELs for compound released from devices. Interindividual variability is taken into account when deriving HBELs for compounds released from medical device materials. As a default, it is assumed that sensitive individuals in the population are no more than 10-fold more sensitive than an "average" individual. Patients with certain injuries or disease conditions (e.g., infection, fever, shock, trauma, hypovolemia/ may represent a sensitive subpopulation and consequently may be more sensitive to the adverse effects of chemical agents than "average" individuals. OST scientists have developed the scientific justification demonstrating that sick or injured patients are indeed a sensitive subpopulation; but the default factor used 10-fold uncertainty to account for interindividual variability in the general population is adequate to protect critically ill or injured patients from the adverse effects produced by chemical residues released from device materials.

Acute Deafness and Blindness Following Treatment with Aged Dialyzers

Key words: hemodialysis, dialyzers

Within 7-24 hours of hemodialysis treatment using 11.5-year-old dialyzers, seven patients at Hospital A developed deafness, blindness, vertigo, and other severe neurological symptoms.[1] None of the patients fully recovered from their injuries and all seven died within one year. These reactions were unusual in their severity, and there were no symptoms noted during the dialysis treatment. These reactions were not like the typical adverse reactions reported due to bacterial contamination, improper disinfection, or ethylene oxide-induced anaphylactoid reactions. Only the patients dialyzed with the 11.5-year-old dialyzers developed the symptoms: other patients dialyzed on that same day with other dialyzers did not develop any symptoms.

The CDC and the FDA investigated the incident at Hospital A. After the preliminary investigation, it was suspected that the dialyzer membrane degraded over its long storage period and that the degradation products caused the patient injuries after being introduced in the blood. Other much less severe incidents involving eye injuries have been reported and were attributed to the membrane degradation product, cellulose acetate oligomers.[2] In order to determine the cause of the incident at Hospital A, cellulose acetate dialysis membranes of ages up to 14 years were retrieved from the public and tested for membrane integrity. It was found that membranes have significant decreases in average molecular weight, undergo some deacetylation, and produce leachable degradation products as they age. The degradation products were isolated from old dialyzers and also made synthetically to confirm the chemical structure of the suspected causative agent.

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[1] Neumann ME. CDC puzzled over neurological disorders at Alabama dialysis unit. Nephrology News and Issues 10(11):9,11 November 1996.

[2] Oba T, Tsuji A, Nakamura A, Shinitani H, Mizumachi S, Kikuchi H, Kaniwa M, Kawasaki Y, Furuya T, Matsumoto K, Tobe M. Migration of acetylated hemicellulose from capillary hemodialyzer to blood, causing scleritis and/or iritis. Artificial Organs 8(4):429-435. 1984.

The degradation products were injected intravenously into the New Zealand white rabbit, and injuries similar to those observed in the patients at Hospital A were reproduced.

As a result of this incident, the FDA, in cooperation with industry, standard organizations, and health care providers, is developing shelf-life criteria for these devices. The FDA also now requires a date of manufacture to be indicated on the labels of all new dialyzers.

The Effect of Fold Flaws on Breast Implant Shells Failure Characteristics

Key words: silicone, mammary implants, polymer degradation, fatigue

In order to determine whether the failure characteristics of elastomeric breast implant shells are dependent on fold flaws, randomly selected samples from manufacturers' lots were subjected to a bi-directional cyclic stress. Circular samples of the shell material (polydimethylsiloxane) were placed in a specially designed test apparatus which provides constant-volume sinusoidal displacement of the membranes, while simultaneously allowing monitoring of a transmembrane electrical signal. As stated in previous reports, membrane integrity) which is detected by the electrical signal and confirmed by visual changes in elastomeric membrane's physical properties are reflected in corresponding alterations of the electrical signal. The samples were fatigued until frank failure (loss of inspection/microscopy. Tested samples were mounted onto the system in two configurations: flat and folded. The flat configuration was defined as the membrane's original form as received from the manufacturer, not actually flat but possessing a slight curvature. The folded configuration places an S-shaped fold (of a defined width) at the center of the test sample. Both sample populations were tested under the same experimental conditions.

Initial experimental results clearly demonstrate that topology does effect the failure characteristics of breast implant shells. The mean values of "cycles-to-failure" within the two populations were not the same, with flat specimen lifetimes an order of magnitude longer than folded. Flat sample lifetimes exceeded 5,000,000 cycles, whereas folded samples exhibited lifetimes ranged between 252,000 and 520,000 cycles (mean lifetime < 390,000 cycles). Differences in the fatigue lives for the two sample configurations were so pronounced that flat samples, which failed from abrasive contact with the test cell's holding mechanism during the initial phases of the experiment, demonstrated longer lifetimes of 1,100,000 cycles. (This design problem was corrected.) Along with these findings, the additional observation of polymer-on-polymer abrasion occurring provides further insight into the material's failure mechanism. Failure of the implant shell with fold flaws can be seen as resulting from the combination of fatigue stress, torsional forces, and abrasion. The observation of polymer-on-polymer abrasion and its resulting debris during these experiments provides an explanation for the presence of material described as "sand" or "sand-like" in various clinical papers on explanted shell material.

Data analysis of the transmembrane signal is expected to allow for the characterization of possible electrical signatures that predict the onset of frank membrane failure. Initial results verify previous work done in this area and it is hoped that a complete analysis of the waveform data might lead to a predictive capability. Fatigue lifetimes for folded/creased shells will be shared with OSB, due to the direct relevance of the presence of "memory folds"/fold flaws *in situ* to earlier onset of clinical leakage. The preliminary

OST results add confirmatory support and show why small tears are associated with shell infoldings, "fold flaws."[3] In our studies fold flaws eventually lead to tears. Enhanced MRI can visualize fold flaws *in vivo*, providing the capability of identifying implants whose lifetimes have been shortened.

Environmental Degradation of Latex Rubber Gloves

Key words: latex gloves, environmental, standards

The research objectives were to assess conformance to standards of latex medical gloves at the point of use and to assess the influence of environmental conditions on the aging characteristics of natural rubber latex gloves. The Washington State Department of Health Board of Pharmacy is under contract to FDA to complete this study. The Program for Appropriate Technology in Health (PATH) is the principal investigator for the Board of Pharmacy. This study consists of two phases and is scheduled to be completed in August 1999.

Phase I of the study assessed the current status of glove sources, prevalence, and user opinion in a cross-section of service delivery modalities and geographic locations within the state of Washington. Service delivery categories were based on 16 Standard Industrial Classification categories, with 68 visits made to providers in 15 of the categories, including doctors of medicine, dentists, nurses, hospitals, and ambulatory surgical services. A total of 168 health care workers who used gloves were interviewed. A wide diversity of gloves were being used. While users generated many comments, nothing definitive could be concluded about specific brands or quality. Based on the variability of inventory practices found, it appears that a number of health practitioners and glove users would benefit from general glove logistics guidelines, specifically in terms of inventory rotation and storage practices.

Phase II of the study includes examination of baseline conformance to glove standards and characterization of aging at different temperatures (22°C, 45°C, and 70°C) for 26 different brands of natural rubber latex gloves. The 26 brands represent various countries of origin and surface treatments (powdered, powder-free, "chlorinated" and sterile). To date, the study results confirm that many of the chlorinated gloves have a severely reduced life at elevated temperatures when compared with the other types of gloves. Also, the frequency of holes (water leakage) in different parts of the gloves was measured. After exposure at 70°C for 100 days, no correlation was found between the presence of holes as determined in the water leakage test and the length of accelerated aging.

Phase II will also examine the effect of oven-aging on static viral permeability and establish viral permeability of samples after they have been stressed in a flex-fatigue cell.

Monocyte/Macrophage Interaction with Particulates

Key words: monocytes, macrophages, aseptic loosening, particles

[3] Gorczya DP. The Augmented Breast: Radiologic and Clinical Perspectives, Gorczya DP (Ed.), Thieme Medical Publishers, New York, NY, Chapter 9, p. 137, 1997.

Aseptic loosening of total joint replacements is the leading cause for revision surgery. Wear debris particles generated at the articulation between the plastic and metal components of a device activate phagocytic cells, such as monocytes and macrophages, which initiate a cascade, resulting in osteolysis and aseptic loosening. The exact mechanism by which the particles cause the loosening is unknown. However, factors such as size, shape, particle load, surface morphology and other physio-chemical factors contribute to the process. OST has prepared batches of endotoxin-free, commercially pure titanium, polymethylmethacrylate, and polystyrene particles to interact with human monocyte-derived macrophages. These studies include phagocytic uptake, the production of reactive oxygen species (as measured by chemiluminescence) and FACS cell sorter analysis of cell particle mixtures. Planned experiments also include studying the activation of early gene products and production of early proteins as a corollary of monocyte activation (study to be performed with CBER). A poster was presented at Catholic University (May 1998) and an oral presentation to the OST/DMMS staff (June 1998).

Effect of Oxidizing Environments on Biomaterials

Key words: oxidation, oxidative, pyrolytic carbon

Methods for assessing the potential for material degradation which could lead to device malfunction based on the characteristics of the materials, and the interaction with the host can greatly aid in regulatory decisions. Real-time cellular-materials interactions assays and imaging can provide critical information for qualification of materials and devices and their environments, especially in terms of their functionality and durability. OST has developed a protocol for oxidizing pyrolytic carbon using biologically relevant oxidants. Scientists used a combination of techniques, including cell-materials interactions to measure oxidative species production by chemiluminescence (CL) and surface analytical techniques (X-ray Photoelectron Spectroscopy (XPS)), and Time of Flight SIMS (NESCA, U. Wash.)) to study the mechanisms of cellular degradation of pyrolytic carbon. These techniques include incubating human monocyte-derived macrophages with pyrolytic carbon for various periods of time to determine if oxidation of the carbon surface can be detected following these treatments. XPS analysis appeared to indicate increased oxidation of the pyrolytic carbon surfaces by the human monocyte-derived macrophages. However, the presence of residual protein from the cells and media has necessitated that additional experiments be performed to determine the source of the oxidation.

Study of Naturally Aged Latex Gloves

Key words: latex, gloves, shelf life, chlorination, tensile test

Latex exam gloves that have naturally aged up to 5 years since the date of manufacture will be studied. The gloves will be subjected to tensile testing (per ASTM D 412) and water leak testing (per ASTM D 5250) to assess the level of deterioration in tensile strength, elongation, and leak resistance that occurs with natural aging of the product. It is known that some glove formulations have been altered in recent years to lower the protein and/or powder content of the finished product. Thus, caution will be exercised to study only brands for which the formulation has not significantly changed over the period of interest. Results of this research will provide insight into the determination of shelf

life for natural rubber latex gloves. Of primary interest is the degree to which chlorinated gloves maintain their strength relative to other glove formulations (e.g., powdered and powder-free nonchlorinated). Collection of the gloves from various sources has been completed. Physical testing will begin once the necessary equipment modifications are finished.

The Effect of Sodium Azide on the Strength of Synthetic Absorbable Sutures *In Vitro*

Key words: suture, sodium azide, mechanical testing, standards

As an initial step in the development of an *in vitro* test method which can be used as an alternative to an *in vivo* test for determining the degradation in the strength of absorbable sutures as a function of time, it was necessary to identify any effect of sodium azide (an antimicrobial agent) on the *in vitro* strength of the sutures. Five types of size 3-0 synthetic absorbable sutures were examined: Dexon II, Vicryl, and Polysorb, which are coated and braided, and two types of monofilament sutures: PDS II and Maxon. Dexon II is composed of polyglycolic acid (PGA) while Vicryl and Polysorb are composed of copolymers of glycolide and lactide. PDS II is composed of polydioxanone and Maxon is composed of polyglyconate. The mean knot tensile strength was determined for each of the five types of sutures initially out of the package and after 1, 2, and 3 weeks of immersion at 37'C in sterile phosphate buffered saline (PBS) alone and in PBS + 0.1% sodium azide, both solutions at pH 7.4 ± 0.2.

In all cases, except for the monofilament sutures PDS II at 3 weeks and Maxon at 1 week, the mean knot strengths for sutures incubated in PBS alone were within one standard deviation of the values for sutures incubated in PBS with sodium azide. A t-test (with a significance level of 0.05) showed no difference between mean knot strength values for sutures incubated with and without sodium azide, except for the PDS II sutures at 3 weeks. The monofilament sutures showed a larger standard deviation in strength values than the braided sutures and failed away from the knot more frequently, indicating that a different test protocol may be more appropriate for the monofilament sutures. However, the results demonstrate that sodium azide can be used as an antimicrobial agent in extended degradation tests of these absorbable polymers without concern that its presence will affect the mechanical strength of the samples.

OPTICS

Diffuse Reflectivity of Tissue: Determining Optical Characteristics and Surface Photochemistry of Skin and Mucosa

Key words: UV radiation, tissue fluorescence, optical fibers

Diffuse reflectivity measurements offer promise as a means to evaluate the optical properties of tissue and to characterize their response to ultraviolet radiation exposure. In skin, the details of the erythemal response, particularly as a function of skin type, are not fully understood. Also, several medical devices in the pre-IDE and IDE stage of development use analysis of UV-induced fluorescence to diagnose cancerous and dysplastic lesions of mucosal tissues. In contrast to skin, however, mucosal tissue lacks a

protective stratum corneum and melanin and exhibits a rich vascular bed close to the surface. The *in vivo* response of mucosal tissue to UV radiation is unknown.

An interdivisional project has been initiated within OST that is designed to determine the erythemal response from different skin types. Also, a project was begun to study the response of mucosal tissues to optical radiation, particularly in the UV range. Initially, the optical properties of oral mucosa will be determined by radially resolved diffuse backscatter measurements and compared to skin values.

OST scientists have designed and constructed a non-fluorescing, optical fiber to deliver optical radiation to the target tissue. Light is collected via an optical fiber probe that was designed with a variety of source/detector separations. The fiber probe is depicted in **figure 5**.

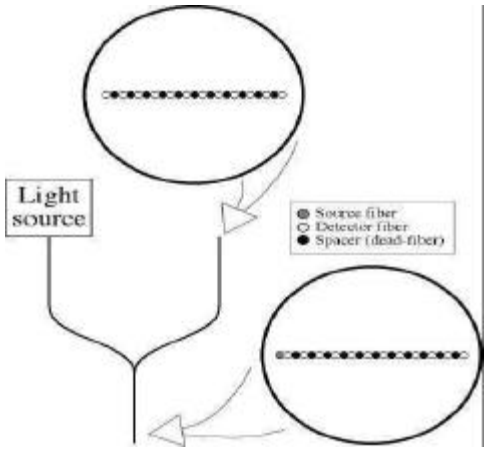

Figure 5. Schematic of fiber probe for studying the diffuse reflectance of tissue in short wavelength visible and near-ultraviolet. The 200-μm quartz fibers are mounted in stainless-steel ferrules and fixed in carbon-laden epoxy.

By permitting resolution of several source/detector separations simultaneously, this geometry can be used in conjunction with an appropriate mathematical model of light transport to deduce bulk optical properties of tissue. Initial studies have characterized the fiber probe by evaluating the spatial distribution of light emerging for volunteer subjects' forearms when illuminated with single frequency green light. A three-dimensional rendition of the image of detector fibers is shown in **figure 6**. The deep hole indicates saturation of the detector at the fiber closest to the sources. Shallower troughs show decreasing detected intensity at further distances from the source fiber.

From this image, the detector fiber brightness as a function of separation from the source fiber can be determined **figure 7**. Curve-fits of the brightness vs. radial distance data provide values for μ_t and μ_{eff}, the total and effective brightness, respectively.

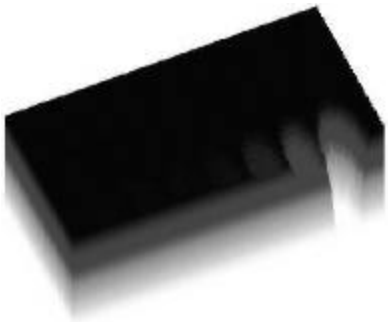

Figure 6. Three-Dimensional Detector Image. Three-dimensional rendition of the image of the "detector" end of the probe when the "target" end is in contact with and illuminates a subject's forearm with 543 nm light.

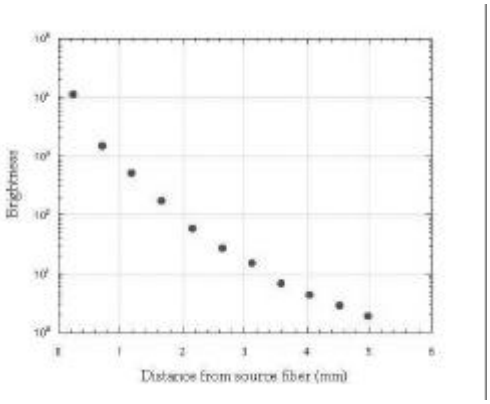

Figure 7. Plot of the spatial distribution of light migration from source fiber to detector fibers. Curve-fits of brightness vs. radial distance data provide values for μ t and μ eff (total and effective).

Studies are underway to evaluate the spectral response of the fiber/probe combination and the actual spectral irradiance delivered at the probe contact surface. In addition, the stability of the spectral response will be established following a disinfecting protocol. After the initial studies, a pilot study will be conducted to compare mucosal tissue with skin tissue. Data acquired will yield an estimation of volume light distribution as a function of wavelength for mucosal tissue as compared to skin tissue. If the penetration depth of optical radiation in mucosa differs from that in skin as suspected, guidance specifying the differences will be prepared for ODE reviews.

Intraocular Lenses

Key words: intraocular lenses, myopic implants, technical support

OST scientists have been collaborating with staff from ODE, experts from industry, and representatives of ophthalmic professional societies to agree upon definitions and testing protocols for clear-lens implants for treating myopia. These implants are a recent offshoot of the highly successful intraocular lens (IOL) implant used after cataract surgery. Clear lens IOLs are being tested as a method to replace eyeglasses for people whose refractive errors are too large to be adequately handled by either spectacles or laser surgery. When an IOL of this type is implanted, no cataract surgery is performed. Instead, the implant is placed directly in front of the natural lens, either just in front or just behind the iris. There are thousands of individuals whose vision would benefit from successful use of such an implant. In these cases, either the spectacles are extremely thick and work only for central vision or spectacles provide no useful correction because of differences between the two eyes. Current laser techniques are not stable for these large refractive errors.

The testing regimen developed during international standards work on conventional intraocular lenses was a natural starting point. The key definitions of power and resolution could be taken directly from the existing document. However, the small size and high negative powers of these lenses posed some new challenges for obtaining the quantities specified in the standards. These difficulties were resolved by the use of computer ray-trace techniques in a model that simulated the human eye. This simulation also provided a useful platform for predicting the correct implanted power.

The existing IOL standard allows for a variety of measurement techniques to specify lens power, each with its own limitations. The approach taken by OST was compared to one taken by a clear-lens sponsor. After testing at the factory, IOLs for myopia were tested in OST and then sent to an independent testing laboratory. The results of these three sets of tests were found to agree within experimental uncertainties. Thus, the robustness of the conventional IOL standards was demonstrated in even this extreme case of high negative lens powers.

Noncoherent Optical Radiation Program

Key words: UV radiation, calibrations, technical support

During 1998, OST continued to provide support to the optical radiation compliance program through consultations on optical radiation measurements. The OST laboratory maintains equipment for conducting high precision optical radiation measurements. Laboratory measurement instrumentation is calibrated using a standard of spectral irradiance which has been calibrated by NIST (National Institute of Standards and Technology). To assure the validity of measurements made by OST, periodic intercomparisons are also conducted with NIST, and in-house quality assurance procedures are followed. During the latter part of October 1997, the optical radiation measurements laboratory was relocated to a new building. The laboratory was reconstructed in a manner to ensure the continued high precision of the measurements program. It is anticipated that an intercomparison with NIST will be conducted during the first half of FY 99.

In FY 98, OST scientists acquired and tested a second-generation field portable spectroradiometer system. This system is being used not only for laboratory measurements of noncoherent light sources, but also to assist in conducting an intercomparison of measurement capabilities with FDA's Winchester Engineering and Analytical Center (WEAC). WEAC assists the Center in performing measurements of light sources collected from manufacturers and other field locations.

In addition, OST personnel consulted with NCTR personnel about how best to equip the new FDA phototoxicity testing center being constructed at NCTR. OST recommended the type of equipment for measurements and calibrations and will provide measurements traceability to NIST for NCTR through biannual intercomparisons.

OST performed spectral measurements and evaluated the suitability of a solar simulator for the Center for Drug Evaluation and Research. This simulator is being used to evaluate a new, transgenic mouse model for photocarcinogenesis research. In its original configuration, the simulator was found to be unsuitable, and additional filtration was recommended and evaluated by OST personnel.

In 1998, OST continued to provide support to the OC through the laboratory evaluation of products which emitted optical radiation. OST evaluated a general-purpose compact fluorescent lamp, for excessive ultraviolet (UV) radiation emissions. Although there was a consumer complaint of a skin burn, OST's measurements did not indicate that a UV exposure hazard existed for typical exposure situations. At the request of a consumer with a history of melanoma, OST evaluated the protective effect of automobile window

films. Spectral transmittance measurements were performed and an equivalent 'SPF' was calculated and provided to the consumer.

Also in FY 98, OST scientists participated in the work of the IESNA/ANSI Z311 committees working on two draft Standards: (1) RP 27.2 Recommended Practice for the Measurement for Risk Group Classification and Hazard Analysis, and, (2) RP 27.4 Recommended Practice for Sunlamps. This work continues the participation of OST scientists in the 1997 work of the ANSI Z311/Illuminating Engineering Society of North America (IESNA), which adopted two optical radiation performance standards for lamps and lamp systems. They are (1) RP 27.1 Recommended Practice for Photobiological Safety for Lamps and Lamp Systems (General Standard), and (2) RP 27.3 Recommended Practice for Photobiological Safety for Lamps: Risk Group Classification & Labeling (Bare Lamp Standard). RP 27.1, is a general standard for photobiological safety and is applicable to all lamps and lamp systems. It defines quantities and terminology, exposure limits, and among other requirements, specifies test conditions, and labeling and technical information requirements. RP 27.3 is applicable to photobiological safety of lamps only. It classifies lamps into lamp safety groups according to the degree of optical radiation hazards associated with the lamps. The standard also specifies labeling and technical information requirements.

Pulsed Xenon Lamps

Key words: optical radiation, optical standards,

In FY 98, OST initiated work, in collaboration with the US Army Center for Health Promotion and Preventive Medicine (USACHPPM) at Edgewood Arsenal, to test and evaluate the optical radiation emissions from products that use pulsed Xenon lamps. Initially, a laboratory-based spectroradiometer was developed to measure the integrated spectral radiance of pulsed light sources. This spectroradiometer was used to evaluate a pulsed Xenon lamp having the potential to expose the public to hazardous levels of optical radiation. Following this evaluation, it was deemed necessary to test additional pulsed lamp sources. Some of these sources would have to be measured in the field. Therefore, in 1998, OST scientists developed a spectroradiometer which was portable and could be transported to the locations of products to be tested in the field. Work will continue on this project in FY 99.

RISK ASSESSMENT

Risk Assessment Activities to Support ODE Reviews, OSB Ad Hoc Committees, and Standards Development

Key words: risk assessment, safety assessment, ODE, OSB, standards

OST serves as a resource to the rest of the Center for risk assessment expertise. During FY 98, OST scientists conducted risk assessments in support of ODE review activities. For example, staff assessed the cancer risk from exposure of the cervical mucosa to ultraviolet radiation emitted from a diagnostic device. Risk or safety assessments were also conducted for specific chemical compounds released from medical devices, in particular, intracranially implanted devices. In addition, because of the recent interest in the potential health effects

from exposure to phthalate esters in consumer products, OST initiated a risk assessment for diethylhexyl phthalate released from medical device materials. Engineers developed a procedure to assess the production of cyanide from laser ablation of uric acid stones at the request of a CDRH ad hoc committee.

In FY 98, risk assessments conducted by OST staff were used by standards setting bodies to develop consensus standards for biocompatibility testing or infection control. For example, the microbial risk assessment activities described above formed the cornerstone of the Sterility Assurance Level standard being developed by AAMI. In addition, risk assessment methodology was developed by OST staff as part of the ISO draft standard on an approach to derive allowable limits for compounds released from medical device materials (ISO/DIS 10093-17).

STANDARDS DEVELOPMENT

Abrasion of Coatings Using a Taber Abraser

Key words: abrasion testing, standards, coatings

A draft standard for abrasion testing of coatings based on past research and test development was finalized for ASTM. In addition, an interlaboratory study was undertaken using ASTM E691. Results were reported by six laboratories for three coatings using four different wear parameters. A proposed Precision and Bias based on those results was calculated, although some changes are under consideration. From this work, the following conclusions have been drawn:

- The ILS study produced a very usable Standard and Bias statement

- The round robin was run without stringent controls on temperature and humidity. Because these controls were not observed and the round robin was successful, it is suggested that these controls be changed to a simple report of these values.

- The ILS study showed that the efficiency of the ultrasonic cleaner can affect the results and perhaps a particular type of US cleaner should be suggested.

- An ILS study was successfully run with returns from six labs on three coatings for four separate cycle levels. Five values for each cell were determined. All this produced an ILS study sufficiently large to produce a precision and bias statement for the draft standard using E691.

Analysis of Operating Microscopes and Endoilluminators

Key words: operation microscopes, cataract surgery, retinal injuries, standards

OST scientists have participated in two studies of the incidence of retinal photic injuries from operation microscopes. One of these studies showed that 28% of patients received retinal photic injuries during cataract surgery. The other study, in which care was taken to reduce retinal light exposure and the risks of retinal injury, did not produce any retinal injuries. The results of these studies have shown that the incidence of retinal photic

injuries from operation microscopes can depend upon several factors. The primary factors appear to be 1) the characteristics of the light source in the operation microscope, and 2) use conditions, such as the length of the operation and whether or not care is taken to reduce the exposure time. Nonetheless, since there are 1.3 million cataract surgeries performed each year in the United States, the number of patients receiving retinal injuries could be significant. In response to this concern, CDRH issued a Health Advisory in 1995 on the risks of retinal photic injuries from operation microscopes occurring during cataract surgery.

In addition, there are reports of retinal photic injuries occurring from intraocular illuminators (endoilluminators) used for ocular illumination during retinal surgery. While the number of patients exposed per year to endoilluminators is substantially less than those exposed to operation microscopes, the reports indicate that a more significant retinal injury may occur from endoilluminators than from operation microscopes. This is probably due to the longer exposure times used during retinal surgery when compared to those in cataract surgery.

This project was designed to evaluate risk reduction techniques from ophthalmic instruments and was conducted in collaboration with ophthalmologists at the National Naval Medical Center (NNMC). The data obtained will be used in the ANSI and ISO standards development process for ophthalmic instruments. It is expected that the use of these standards will result in a reduction of the risks of retinal injuries from these devices and assist in the review of premarket applications.

In FY 97, OST conducted a laboratory evaluation of the risks of retinal photic injury from the optical radiation emissions from endoilluminators used during vitreo-retinal surgery. In FY 98, the results of this study were presented at an international symposium on the measurements of optical radiation hazards and also served as the basis for an agreement to develop a draft ISO optical radiation safety standard for endoilluminators.

Additionally in 1998, OST completed an image analysis for both coaxial and oblique illumination settings from the operation microscope with the use of a model eye. The geometry of the coaxial beam resulted in a small spot of approximately 2 millimeters in diameter on the retina, as was expected. The oblique illumination beams also produced spot sizes of approximately the same dimensions, though at locations distant from the coaxial beam. Image analyses was also done for the aphakic condition (lens removed from eye), and for the situation where an air bubble is injected under the cornea. OST concluded that an increase in safety results, which is proportional to the ratio of the total exposure time to the total exposure time minus the time of use of oblique illumination.

CDRH scientists also collaborated with WEAC in a survey of the optical radiation characteristics of operating microscopes currently in use in the U.S. A survey of several operation microscopes currently in use in the U.S. was completed, and an internal research report was written. This report concluded that the biologically effective intensity of the measured devices is generally lower than that of devices which were evaluated in the early 1990's. Interviews with hospital staff indicated that typical exposure times during cataract surgeries had not changed significantly over the past 10 years. Certain procedures can still last in excess of 1 hour.

In FY 97, OST initiated work to evaluate the use of short wavelength cut-off filters and an adjunct light source (in collaboration with ophthalmologists at NNMC) for reducing the risks of retinal photic injury from operation microscopes. This work was continued in FY 98. A number of different cut-off filters and fiber optic light source designs were developed and evaluated using an operation microscope at NNMC. Although an optimum design of filters and light source has not yet been achieved, work continues to support the idea that the use of filters and an adjunct light source can reduce the risks of retinal photic injury from ophthalmic instruments.

OST continued to actively participate in the development of ANSI and ISO performance standards for the quality of the optical radiation emissions from ophthalmic diagnostic instruments, operation microscopes and endoilluminators. In CY 97 ISO adopted a quasi-horizontal standard for ophthalmic instruments (ISO 15004 (1997)). In 1998, a number of product specific standards for ophthalmic instruments were adopted by ISO. They include standards for Chart Projectors (ISO 10938), Slit Lamps (ISO 10939), Fundus Cameras (ISO 10940), Direct Ophthalmoscopes (ISO 10942), Indirect Ophthalmoscopes (ISO 10943), Synoptophores (ISO 10944).

Also separate draft ISO standards for the light hazards and mechanical/optical performance for operation microscopes (Draft Standard for Optical Radiation Safety - ISO/DIS 10936-1 & 2) were submitted to national committees for approval in 1998. Finally, the draft standard for Endoilluminators - Draft Standard for Optical Radiation Safety – was submitted to ISO for circulation as a Committee Draft (CD) to national committees for approval. Standards conformance assessments were performed by OST of the ISO ophthalmic instrument standards for use in the new CDRH 510K paradigm. Parts of these standards were deemed appropriate for use in 510K clearances for all diagnostic ophthalmic instruments.

Apnea Monitor Physiologic Waveform Test Method Development

Key words: apnea, physiologic waveforms, standards, test methods

The Apnea Monitor Physiologic Waveform Test Method Development project is intended to provide CDRH and the medical device community with a standard bench-test method for determining the ability of an apnea monitor to detect apnea (the cessation of breathing) and its physiologic consequences. In this effort, OST engineers are working with clinicians and manufacturers through a committee of the Association for the Advancement of Medical Instrumentation (AAMI), the Apnea Monitoring Committee, which is co-chaired by the CDRH representative. This multi-year development project consists of the following steps:

- Design, development, and construction of a signal and data acquisition system for recording high-fidelity physiologic waveforms (signals) from infants in sleep labs.
- Collection (recording) of a comprehensive set of physiologic waveforms (signals) from infants in clinical sleep labs.
- Annotation of the collected waveforms by a panel of experts.
- Assembly of the annotated waveforms into a database.

- Design, development, and construction of physiologic parameter simulators to play back the recorded physiologic waveform database to the sensors of the apnea monitor under test. The recorded waveforms will be used to control electrical and mechanical simulators of the physiologic parameters. These simulators will be connected to the apnea monitor under test in place of the patient.

FY 98 engineering effort again focused on the development of signal acquisition software and hardware. Extensive revisions were made to the acquisition system user interface software, and the user interface software was completed.

The acquisition computer, video recorder, tape drive, serial interface card cage, power supply, and isolation transformer were installed in an EMC-rated equipment rack. The equipment installed in the rack was tested for leakage current and found to meet applicable limits.

Patient supplies were obtained, as well as six delta-sigma, analog-to-digital converters (ADCs). Fabrication and packaging of ADC channels for six sensors was in progress, including signal conditioning and serial data transmission, for impedance, ECG, end-tidal CO_2, expired/inspired air temperature, and two annotation-quality pulse oximetry channels, SaO_2 and pulse wave.

Analog output interface cables and connectors were fabricated as necessary to meet the principal investigator's signal recording needs for the pilot clinical signal acquisition.

A second inductance plethysmography monitor interface was installed in a second (newer) inductance plethysmography monitor. The newer monitor was used to characterize the performance of the wideband inductance plethysmography channels. It was determined that absolute calibration in terms of cross-sectional area was not possible. Instead, measured inductance values will be related to circumference measurements taken from study subjects at the beginning of each study.

Developing Standard Methods for Evaluating the Blood Damage Potential of Materials Used in Medical Devices

Key words: hemolysis testing, blood damage, cardiovascular medical devices, standards

In accordance with international standards for assessing the biocompatibility of blood-contacting medical devices (e.g. oxygenators, tubing, catheters, artificial hearts), the individual materials used in devices are evaluated using a battery of cell-response tests. These tests include an *in vitro* assay to determine the material's potential to destroy red blood cells (hemolysis). The usefulness of the current hemolysis standards is being reviewed as part of the FDA effort to recognize testing standards which manufacturers can use to demonstrate safe and effective performance of their materials and devices.

OST has participated with four other testing laboratories on a project to revise and validate the ASTM F756 standard entitled "Standard Practice for Assessment of Hemolytic Properties of Materials", a widely used standard for blood-damage testing. This document is the basis for the international standard on hemolysis testing as well (ISO 10993-4: Biological evaluation of medical devices – Part 4: Selection of tests for

interaction with blood. Amendment 1: Annex D – Evaluation of haemolytic properties of medical devices). The goal of this project is to evaluate the current testing protocols and to create a revised standard test which is easy to perform, appropriate for all materials, sensitive, and has a validated pass/fail quantitative criteria for acceptance of a material.

The currently used protocols for performing hemolysis tests on materials were developed over 20 years ago. The basic hemolysis assay consists of placing a test sample of material taken from the finished, sterilized device into a test tube containing isotonic saline and rabbit blood of known hemoglobin concentration. The tube is incubated at 37°C for up to 4 hours, at which time the material is removed and the plasma is obtained after centrifugation of the tube. The amount of hemoglobin that has been liberated into the plasma from damaged red blood cells is quantified using a spectrophotometer. Since the 1970's, the criteria for classifying a material as being "non-hemolytic" is that the amount of liberated hemoglobin in the plasma be less than 5% of the total available hemoglobin concentration in the tube. The widespread use of this "5% hemolysis acceptance criteria" needs to be validated especially since changes have occurred to the original testing protocol over time (e.g. type of anticoagulant used, blood concentration in tube, material surface area to blood concentration ratio, time of incubation, etc). Unfortunately, the use of the "5% hemolysis acceptance criteria" has propagated throughout testing laboratories and is often used inappropriately in evaluating hemolysis testing of both materials and devices.

In 1998, the OST team rewrote the testing protocol for the current ASTM F756 standard. The purpose was to increase the test sensitivity, perform preliminary experiments to identify negative and positive control test materials, prepare uniform-size sample materials and hemoglobin reference standards for the Phase I interlaboratory evaluations, and participate in the Phase I testing and data analysis. Five laboratories completed testing using the revised ASTM testing protocol and the OST material samples. These samples included a negative control material (high-density polyethylene,), a "low"-positive control material (Buna N nitrile rubber – a copolymer of butadiene and acrylinitrile), and a "high"-positive control material (Copper sheeting). **Figure 8** shows the OST results of testing these materials in triplicate on each day, with the percent hemolysis being greatest for the copper (14-19%), followed by the Buna N rubber (1.8%), and lowest for the tubes which contained either the polyethylene samples or no material at all (0.7%).

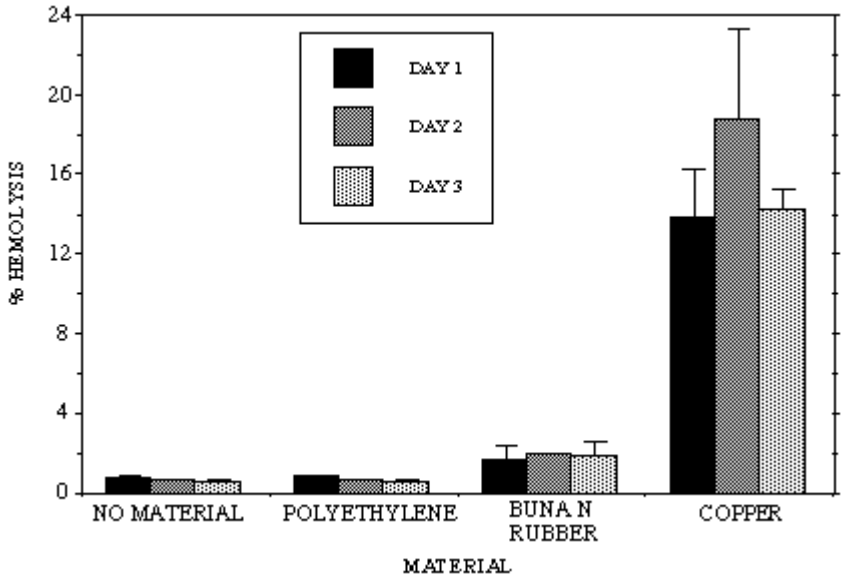

Figure 8. Percent of hemolysis of various materials by revised ASTM test method

In 1999, OST will participate in the planning and testing of the Phase II interlaboratory study to explore the critical parameters which need to be controlled to make a useful standard for testing hemolysis caused by materials. This includes evaluation of the following: different blood anticoagulants, media solutions, blood concentrations, material surface areas, time course of damage, positive control materials, use of extracts from materials, reproducibility of the test within and between laboratories, chemical factors which can alter red blood cell membranes or can interfere with the measurement of hemoglobin, biologic variability of blood from different animals, percent hemolysis classification criteria, and measurement techniques of total and plasma hemoglobin. Along with other concurrent OST projects, the results of this study will help to better define the *in vitro* test limits for evaluating chemically and mechanically induced hemolysis by devices.

Development of a Standard Practice for Testing for Whole Complement Activation in Serum by Solid Materials

Key words: *complement activation, medical materials, standard.*

Complement activation is a potential hazard when patient blood contacts medical device materials. Inappropriate activation of complement by blood-contacting medical devices may have serious acute or chronic effects on the host. This practice provides a protocol for simple, inexpensive, rapid, *in vitro* screening for whole complement activating properties of solid materials used in the fabrication of medical devices that will contact blood. The practice is designed to be used with other standards that assess the biocompatibility of materials. The practice is composed of two parts. In the first part, human serum is exposed to a solid material, during which complement activation and depletion of key complement proteins may occur. In the second part, the remaining complement proteins are assayed as to their ability to lyse antibody-coated sheep red blood cells. This assay determines the functionality of the remaining complement system versus immunological assays that identify the amount of particular components in the blood. In this fashion, complement is determined to not only be present, but to be able to

exert its terminal function: the lysis of target cells. Assessment of *in vitro* whole complement activation as described here provides one method for predicting potential complement activation by medical materials intended for clinical application in humans when the material contacts the blood. This *in vitro* test method is suitable for adoption in specifications and standards for screening solid materials to be used in the construction of medical devices intended to be implanted in the human body or placed in contact with human blood. The draft Standard Practice has been submitted to the ASTM Committee F-4 on Medical and Surgical Materials and Devices via the Subcommittee F04.16 on Biocompatibility.

A Digital Particle Velocimetry Validation Technique Using A Dry Powder Variable Linear Motion Model

Key words: flow visualization, DPIV validation model, technical support, standard test method

Digital particle image velocimetry (DPIV) is routinely used by flow researchers and medical device manufacturers to provide two-dimensional mapping that can identify disturbed flow patterns. As such, it provides a powerful tool for studying the safety and efficacy of flow-related devices. DPIV uses cross-correlation analysis on sequential images of seed particles in a test fluid. DPIV is a complex measurement technology that requires validation for the results to be meaningful. OST scientists have developed a simple validation technique that can easily and reproducibly quantify the experimental variables of any DPIV system and software. Some of the important experimental variables include particle seeding, particle type and size, field of view, camera type and resolution, maximum measurable velocity, measured pixel displacement, cross-correlation interrogation area (IA) or sample test area and percentage of IA overlap, and the time window (Δt) between images. This validation method allows one to improve the experimental methods and settings to determine velocity accurately and reproducibly.

The DPIV validation model adapts a commercially available sanding belt mechanism with a D.C. servo drive motor to produce variable linear motion. The replaceable sanding belt is painted flat black and sprayed with an adhesive that secures the dry powder particles. Particles of any size can be used depending on the field of view and flow structure being investigated. For these preliminary studies, salt crystals from 200-400 microns in size were used, with velocities up to 300 microns/second. Two sequential images were digitized from a full frame acquisition video camera using a frame grabber with a Δt of 33 microns/second (standard video frame rate). Cross-correlation DPIV software was used to determine the velocity of the particles on the belt, which are all moving at the same speed, and for comparison with the true velocity as measured with a NIST calibrated tachometer. The D.C. servomotor can operate in the steady motion mode. In addition, pulsatile motion is possible through the input of an analog signal (i.e. arbitrary waveform generator) to simulate, for example, a physiological cardiac flow cycle. Linear speeds of 0 to 1.7 meters/second were achieved with this model with a resolution accuracy of 0.02% and a measurement accuracy of +/-1%.

Since DPIV determines velocity by measuring the distance a particle pattern has traveled divided by the time between acquired images, the absolute accuracy of this displacement measurement is a function of the pixel image resolution and the pixel displacement of the particle pattern. The Visiflow software has the capability of detecting a ±0.5 pixel

resolution, which for a 50-pixel displacement, can result in a theoretical velocity accuracy of ±1%. Other factors affecting this measurement include the field of view (FOV), and the interrogation area (IA) size. The optimum interrogation area is three times greater than the maximum displacement to be measured to ensure that the particle patterns in both images remain within the critical interrogation window. Erroneous vectors are seen when the IA/3 rule is exceeded for the expected displacement. Particle seeding needs to be on the order of 10-20 particles per IA. The general relationship defining the maximum measurable velocity as a factor of some of these critical variables is seen in the following equation:

$$V_{max} = (FOV)(IA)/[(3)(\#pix)(\Delta t)]$$

Test data demonstrated that with a minimum pixel resolution of 0.5 pixels over a 50-pixel displacement (typical for a 128-pixel interrogation area),
a DPIV velocity measurement of ± 1-3% error was achievable for a Δt of 33 ms (standard video rate) and for velocities less than 300 mm/s.

This flow visualization validation model allows one to quantify the affect of experimental variables on the DPIV measured velocity and optimize their particular measurement system for final use. This validation model provides for quantifying steady flow as well as pulsatile flow such as found in human blood flow. The OST scientists, who developed this new methodology, have submitted a patent application on their invention.

Development of Standards for the Detection of HIV and *Mycobacterium Tuberculosis* by the Polymerase Chain Reaction (PCR)

Key words: polymerase chain reaction, PCR, HIV, Mycobacterium Tuberculosis, standard

PCR is a common molecular biology procedure used in biotechnology laboratories for the amplification and detection of nucleic acid (DNA or RNA) sequences. It is used in clinical diagnostic laboratories to aid in the *in vitro* diagnosis of infectious and genetic diseases.

Commercial PCR-based medical device kit applications for the *in vitro* detection of the nucleic acids of infectious microorganisms and nucleic acids associated with genetic diseases continue being submitted to FDA for evaluation. An OST molecular biologist, with PCR laboratory research experience, is leading the development of PCR standard guidelines with ASTM Committee E-48 on Biotechnology in collaboration with DIN (Deutsches Institut fuer Normung = German Institute for Standardization). An ASTM General PCR Standard (E 1873 - 97: “Standard Guide for the Detection of Nucleic Acid Sequences by the Polymerase Chain Reaction Technique”) was published last year. It consists of recommendations, basic considerations, criteria and principles that should be employed when developing, utilizing, or assessing PCR procedures. The OST scientist together with other FDA and diagnostic industry collaborators are presently developing related guidelines for the PCR detection of *Mycobacterium tuberculosis* plus other pathogenic mycobacteria and for the PCR detection of HIV. These standards are being developed for use in any biotechnology laboratory including clinical diagnostic laboratories.

Error Analysis for Three Types of Commonly Used Clinical Methods for Blood Glucose Measurements

Key words: error analysis; systematic error; blood glucose measurement

The three most commonly used methods for determination of blood glucose by clinical laboratories were evaluated: the spectrophotometric (UV-747) method with hexokinase assay, the colorimetric (CL-700) method with glucose oxidase assay, and the electrochemical (EC-CX3 and CX7) method with glucose oxidase assay. Two accredited laboratories independently performed glucose measurements on three NIST human reference standard sera (102.33, 199.93, and 294.65 mg/dLglucose) for 5 consecutive days. Results were evaluated based on random and systematic errors. Systematic errors were obtained by linear least-squares regression. The CL-700 and UV-747 methods have negligible systematic errors compared to the EC-CX7 and CX3 methods. The EC-CX methods have calibration biases leading to 4.5% error. Total imprecision was obtained as coefficients of variation (CV) of 0.62, 0.93, 1.15 and 1.41%(n=150) for CL-700, UV-747, EC-CX3, EC-CX7, respectively. The stability of the three systems was also evaluated.

Genetic Toxicology Testing for Medical Devices

Key words: genetic toxicology, materials testing, guidances.

Evaluation of medical devices for potential adverse biological effects presents unique difficulties. The devices and/or materials are extracted with solvents, and the extracts are subject to testing for the presence of toxic and potentially carcinogenic substances. Typically, the extraction times are short relative to the residence time in humans, and the solvents used are limited in their extraction efficiency. This results in the presence of low concentrations of extractable materials available for testing. Recently, new international guidances for genetic toxicology testing have been developed by both the International Conference on Harmonization (ICH) and the International Standards Organization (ISO). OST scientists have contributed to the development of both of these guidances, the latter of which is devoted specifically to medical devices. In considering the special situation of medical device testing, recommended tests were those with sensitivity adequate to detect low concentrations of genetic damaging agents, and those capable of detecting a comprehensive and complementary range of genetic damage. Several tests used in the past failed to meet these criteria and would be less likely to yield meaningful results.

Natural Rubber Latex Test Methods

Key words: natural rubber, Lowry protein method, glove powder

The use of elastomeric products made from natural latex rubber has increased greatly since the advocating of universal controls by CDC to minimize the spread of AIDS and other blood- or body fluid-borne organisms. The major devices under consideration by OST are medical and surgical gloves, condoms, and rubber stoppers (hard or elastomeric) in syringes and injection vials. With the increased use of these latex products came an increased incidence of allergy to latex. The allergic reactions are often life-threatening. The problem occurs in patients coming in contact with the products, as well as the health care workers with extensive exposure to the products. The cause of the allergic response is proteins that remain with the latex during washing, refinement, and manufacturing of

the devices. It is important to be able to determine the amount of protein on the devices and both a test method and detection limit for labeling protein content in gloves is needed. OST has contributed to the guidance documents, the labeling regulations, and the ASTM standards. The ASTM standard using a modified Lowry method is being revised with extensive round robin testing to make the test more sensitive. In addition, OST is developing the ELISA method, which is based on immunologic detection methods, that will be more sensitive for total protein and will provide the ability to detect the specific proteins implicated in the allergic response. Work will continue in this area.

Although protein has been implicated as the major cause of the allergic reaction to the latex products, there are other health care concerns. The elastomeric latex products are very sticky and difficult to work with. Thus powder is often placed on the surface to facilitate donning and for handling such things as surgical instruments. However, excess glove powder may enhance the allergic response by being an airborne carrier of the protein, or it may contribute to inflammatory responses in tissue. It is important for the health care professional to know the powder content of the gloves. Thus standard methods for measuring powder levels, voluntary consensus standards on type and use of powder, and labeling regulations for "powder free" gloves are all needed. OST has been very active in evaluating the methods, working with the standards development organizations, and promoting the guidance documents and regulations. This will continue.

Protective Clothing

Key words: infectious agents, barriers

Various textiles and synthetic polymeric materials are used as barriers to prevent transport of infectious agents from the environment to the deep tissue. As new products are being developed, it is important to have a simple test method to detect leaks in the barrier materials. A simple test method using viruses for leaks in condoms and surgical gowns has been developed. This will help greatly in evaluating these proposed materials and devices.

Performance Standard for Puncture Resistance of Sharps Containers

Key words: medical sharps, needlestick injury, mechanical testing, standards

A performance standard for puncture resistance is being developed to ensure that medical sharps containers are adequately designed and constructed to withstand puncture forces experienced during use. The standard allows for assessment of puncture resistance via two mechanisms: (1) a direct method based on measurement of puncture force of the container, or (2) an indirect method based on measurement of container thickness, which is correlated with puncture force. FDA participated in an interlaboratory study to assess the precision of these test methods. Test samples included specimens from different “regions of nominal uniform thickness” from two commercial sharps containers and plaques of a specific polypropylene material in five different thicknesses. Needle force was applied and measured using an Instron universal testing machine, with puncture force taken to be the force applied to the needle when it just penetrated the bottom side of the sample. The data generated were analyzed in conjunction with data from other

laboratories for calculation of appropriate precision information (repeatability and reproducibility) to be included in the final performance standard.

Simulator for Use with Pulse Oximeters

Key words: pulse oximeter, simulator

Pulse oximeters are intelligent medical devices that can noninvasively assess the function of the heart and lungs during critical care and surgical procedures. They do this by calculating an indicator of oxygen saturation that is based on measuring the amount of light energy lost in a tissue bed perfused by pulsatile blood. More and more clinicians are coming to depend upon oximeters to issue an alert when a patient is in trouble, resulting in an exponential rise in their use. The ability to assess the performance of oximeters, to ensure their safe and effective operation, including accuracy and immunity to noise and artifact, is therefore very important. The American Society for Testing and Materials (ASTM), the International Standards Organization (ISO), and the European Normalization Committee (CEN) have all addressed the need for a standard to ensure the reliable and safe function of oximeters. All three standards, ASTM F1514, ISO pr9919, and CEN prEN 865 are similar in content, and all three are unable to identify an adequate test method to support their requirements. The ASTM standards committee is currently drafting new requirements. An OST scientist is chairperson of this committee and is addressing the lack of test capability by collaborating with a European consortium to develop an electronic simulator that uses recorded physiological waveforms, adjusted for each oximeter's particular requirements, to challenge (reproducibly and without blood) the performance of the device. The goal of this work is to have all three international standards activities and the FDA regulatory process harmonized by having a single accepted test method used in each.

OST was asked by CEN to provide technical assistance in support of their simulator development efforts. An OST scientist, who served as the Project Officer and principle engineer of the FDA simulator, last year presented to the CEN group (during CEN's biannual meeting in San Sebastian, Spain) the requirements that a simulator would have to achieve to be a useful regulatory tool. The scientist was asked to continue participating and contributing technical guidance until the test method for pulse oximeters was completed and the Standards amended to include it. A collaborative effort is underway to accomplish the following: to record high fidelity clinical waveforms that are representative of the expected physiological information and environmental noise and artifact; to develop a high fidelity, non-blood based simulator; and to develop a test protocol so that both the quality of the calibration of the oximeter and its ability to function in its intended-use environment can be assessed. Based on a design concept developed in a previous FDA contract with the University of Washington, the prototype simulator concept has been demonstrated and a new, higher performing clinical signal collection system has been developed and is in use. To date, 500 data sets have been recorded using this system. OST continues to participate in the development and improvement of the simulator design.

TECHNICAL SUPPORT

The Biomaterials Compendium

Key words: biomaterials, database, materials properties data

The major event of this year was the transition from the development of a free standing PC-based program written by an outside contractor, to an internal Centernet program. The program was developed such that it links the materials information entered by the agency using the Compendium Edit program with manufacturer and device information that exists in the Center's management information system (MIS). To enter materials information for the device, one opens the program, enters the document number, and the program searches the MIS for information on manufacturer, product name, product code (procode), dates of submission and decision, and the decision status. One then enters details about indications for use and sterilization relative to the device. For each component, i.e., material, that makes tissue contact, one then enters the material name, component processing, and tissue contact information. The program also has a search routine, which at this time can search on material name, device name, or document number.

Progress has also been made in populating the database. A "pilot" program was initiated with Ophthalmics, in which they provided detailed information on several products. OST has continued to be part of the BSE committee and involved in the guidance document. The database has been used for tracking devices containing animal-derived products. In addition, the ODE Biomaterials Group was formed and is charged with gathering information about materials-specific issues. These issues are discussed as they pertain to different divisions. Some of this information has also been entered in the database. To date, chlorhexidine coatings and some nitinol products have been a focus of interest. Materials information is to be entered on all active IDE's and PMA's. Additionally, the Biomaterials Group is to identify priority areas of materials and devices where historical data needs to be captured.

Book of Hazards

Key words: device hazards, risk management

Medical device safety issues require consideration of a host of factors involving hazard identification, risk estimation, and mitigation techniques. Over time, individual reviewers and analysts have gathered a great deal of valuable information regarding medical device hazards. Other reviewers may not be aware of this information, understand its importance or applicability to other cases, or know where in the Center to find the information in a timely fashion. Some interchange does occur via informal networking, seminars, meetings, and even happenstance; but there is currently no established mechanism for documenting and sharing such information, leading to inefficiency and inconsistency in the quality of reviews. The Book of Hazards is an Intranet tool designed to collect and improve utilization of CDRH's institutional knowledge of medical device hazards.

A shared database application is under development, residing on the CDRH Intranet, to collect and make available the following information:

- the salient hazards a device would expose a patient or user to;
- the consequences that those hazards present;
- risks associated with the hazards;
- techniques used by manufacturers to mitigate hazards; and
- residual risks.

The information is organized and cross-referenced by device type, technology (e.g., embedded software, pneumatics, patient-contacted electrodes), clinical specialty, general hazard, or other desired field. Each time a device is analyzed, the reviewer/analyst may draw upon the Center's knowledge base by querying the system for hazards identified in the past. The user can concentrate on determining the risks associated with the identified hazards in each particular case and on identifying new hazards that were not previosuly recognized. These new hazards would be submitted to the system improving the completeness and applicability of the knowledge base. As a quality assurance measure, this information would be reviewed by an appropriate technical committee for accuracy and completeness before it is entered into the Intranet database.

Areas of activity are

- Determining what can be used as a unique device identifier.
- Identifying General Hazard Categories. Current plans call for the adoption of hazard categories in ISO/IEC 14971 and the EU's Medical Device Directives. This list is fixed; no new general hazards can be entered by users.
- Investigating the amount of detail in the reports or code books (MDRs may supply a source of Specific Hazards. This list may also be fixed.
- Extracting several of the consequences from the database of Consequences contained in the IML system (formerly Medra or ADROIT) which OSB is purchasing. This list is to be of fixed size.
- Exploring mechanisms for controlling and reviewing information to ensure integrity (correctness & completeness). The demonstration prototype allows only the mitigation and specific hazard list to be extensible; all other fields will be from a fixed set of data. The user will have the option of requesting that new information be reviewed and made available. Current plans are for the branch chief to act as the reviewing function. How the reviewing function will operate (that is, via e-mail or web-based forms) has not be established.

A device, ablation therapy, was chosen as a test subject because it has multiple review components: OB/GYN (uterine ablation) and DCRND/OGDB (cardiac ablation). These two ODE branches have agreed to participate in a demonstration pilot that is designed to determine the level of detail of each of the information fields (specific device hazard, consequences, mitigations) and explore user interface designs. A pilot demonstration program has been completed and results from using the pilot are being used to improve the user interface and make improvements to the specific hazard and consequences tables. The data collected from this pilot will be analyzed to update the draft requirements specification. Current funding provides for two phases of an anticipated three-phase development program. Phases one and two implement a research prototype and have the flexibility to allow information tables and fields to be changed based on user input. Phase three is expected to documents requirements that will allow expansion to a formal CDRH and FDA information system.

Diabetes Electronic Network

Key words: diabetes, communication, tech support.

OST scientists are involved in aiding in the evaluation of safety and efficacy of a variety of diabetes-related medical devices, including clinical test kits, glucose biosensors, extracorporeal glucose sensing methodologies, and insulin pumps. To facilitate FDA-wide interaction on these and other diabetes-related topics, the FDA-wide Diabetes Electronic Network Interest Group was established. The DIABETES distribution list enables any list member to send a message to one central address where the message will then be distributed across FDA to all list members. Thus, members can easily communicate as a group.

An announcement on the new DIABETES peer group communication mode was made through FDA News to all Centers and field laboratories. Over 160 laboratory and review scientists subscribed to the service. The DIABETES e-mail distribution list is actively moderated such that 1) only appropriate messages are distributed to the list (thus minimizing trivial or misrouted messages); 2) messages are well "flagged" as to contents (to provide clear, quickly accessible information); and 3) effective communication is actively encouraged and guided (such that the format is well utilized.)

Activities of the network include the following: 1) provide assistance on product-related regulatory review issues; 2) updating advances in diabetes research and their regulatory impact; 3) discussing news of ongoing diabetes research, methods development and evaluation, and standards activities in the Centers; and iracle4) providing information on meetings, alternative sources of information, and other activities of interest in the application of diabetes research/diagnosis/therapy in regulatory review.

The goal of this effort is to bring laboratory and review scientists closer together, to optimize resources, and to facilitate peer group formation and communication across FDA. A main product is expedition of reviews by providing ready access to a large pool of expertise in all aspects of diabetes research, diagnosis, and therapy.

Isolation of High Molecular Weight DNA from Human Brain Tissues

Key words: DNA isolation, brain

An OST molecular biologist in collaboration with biochemists from the GSF National Research Center for Environment and Health, Munich, Germany, have developed a method for the isolation of high molecular weight DNA from postmortem, frozen, human brain tissue. Development of this method was an offshoot from a previous OST project concerning the detection of HIV in brain tissues (Bockstahler et al., Clinical and Diagnostic Virology 3:61-72, 1995). Samples of frozen brain tissues were ground to a fine powder with morter and pestle in the presence of liquid nitrogen. 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. Each DNA sample was analyzed with a spectrophotometer and examined by agarose gel electrophoresis to demonstrate that it contained high molecular weight 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 procedure could be useful in situations where high molecular weight DNA from brain tissues of deceased humans may be

needed. An example of such a situation is the necessity for FDA or other scientists to perform rapid DNA-based molecular diagnostics to determine the extent of central nervous system infection associated with an epidemic caused by an emerging DNA-containing microorganism. The primary purpose of a report being prepared on this project is to describe the procedure in sufficient detail so that it could be readily reproduced in other laboratories.

Laser Field Compliance Program

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

During 1998, OST continued to provide support to the laser field compliance program through consultations on optical radiation measurements. The activities of OST's laser calibration laboratory provide validity to the measurements made in compliance testing programs nationwide. The OST Laser Calibration Laboratory maintains equipment for conducting high precision optical measurements. The laboratory measurement standard is a C-series calorimeter built by NIST. To assure the validity of measurements made by OST, periodic intercomparisons are conducted with NIST, and in-house quality assurance procedures are followed. During the latter part of October 1997, the laser calibration laboratory was relocated to a new building. Work is continuing to reconstruct the laboratory to ensure the high precision of the laser measurements program. It is anticipated that an intercomparison with NIST will be conducted during the first half of FY 99.

Laser Product Evaluations

Key words: lasers, product testing, technical support

In 1998, OST continued to provide support to the OC through the laboratory evaluation of laser products. The testing is normally performed in order to confirm the manufacturer's classification of the product. OST evaluated 32 laser pointers that had been obtained either as a follow up to an injury report or due to products being detained at the port of entry. With the exception of one unit, all pointers met the Class IIIa limit of the laser product performance standard. OST also evaluated six infrared laser rangefinders, and a visible laser diode module. These products were found to meet their respective Class limits.

Resuscitation Filter Flow Resistance

Key words: resuscitation, respiratory filter, pressure testing

Recent concerns about communicable infectious diseases have led to an increased utilization of protective gear by emergency care providers. One such protective device is a respiratory filter to be placed in line with a patient mask during emergency mouth-to-mouth resuscitation.

At the request of the Office of Device Evaluation (ODE), a brief laboratory evaluation of a new model of resuscitation filter was undertaken to determine if the resistance to flow was equivalent to similar devices on the market. The concern expressed was that the design of this product resulted in a forward flow resistance that is unacceptably high and

might lead to ineffective air exchange in an emergency situation due to rescuer fatigue. As of the time of the evaluation, the 510(k) application was under review in ODE. This laboratory evaluation was requested to assist in the application clearance decision.

Steady-flow pressure drop was measured across four test devices over the range of physiologic flow rates (up to 60 liters per minute), and compared to similar data for five commercially available filters indicated for similar use. Measurements were taken in the forward (rescuer to patient) and reverse (patient exhalation) directions. The new device had a forward pressure drop six (6) times higher than the maximum value for the predicate devices (33 cmH_2O versus 5 cm H_20 at 60 Lpm). Additionally, the reverse pressure drop was marginally within the limit prescribed in the applicable consensus standard for these devices. As a result of these findings, the manufacturer was required to revise the filter design before it was cleared for marketing.

Cleanroom Software Engineering

Key words: software development

OST is working to identify and establish software engineering practices most appropriate for the medical device industry. To this end, OST and the Walter Reed Army Institute of Research are investigating the development of a software-controlled, closed-loop infusion pump system, using the Cleanroom software engineering process, under the U.S. Army's Life Support for Trauma and Transport (LSTAT) program. In particular, OST is involved in the development of a usage model for testing this software system.

Cleanroom software engineering is a theory-based, team-oriented process for developing and certifying high-reliability software systems under statistical quality control. The Cleanroom name is borrowed from hardware Cleanrooms, with their emphasis on rigorous engineering discipline and focus on defect prevention rather than defect removal. Cleanroom software engineering combines mathematically based methods of software specification , design, and correctness verification with statistical, usage-based testing to certify software fitness for use.

X-ray Calibration Laboratory

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

OST is responsible for the traceability of ionizing radiation measurements made by FDA or used in FDA compliance programs to National Standards. This mission is fulfilled by the operation of a secondary standard laboratory accredited by the National Voluntary Laboratory Accreditation Program (NVLAP). In FY 98, a total of 1,786 calibrations of radiation-measuring instruments were performed by irradiation in known x-ray fields. A significant 1,554 of these calibrations fell under the scope of accreditation. In addition, 502 electrical calibrations of the readout circuits and 115 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 98, 66% of the instruments calibrated were owned by FDA, 31% by state agencies, and 3% by other federal agencies. During this time, 72% of the instruments calibrated were designated for testing compliance with the Radiation Control for Health and Safety Act of 1968; another 28% of the instruments were designated for testing compliance with

the Mammography Quality Standards Act of 1992. OST keeps track of approximately 2,800 pieces of equipment at over 500 inspector stations throughout the country and U.S. territories, as well as instrument usage and calibration data. As required by NVLAP, the laboratory this year has participated in a Proficiency Test administered by the National Institute of Standards and Technology (NIST), has undergone an internal audit of operating procedures, and conducted a comprehensive review of the Quality System. The laboratory complies with NIST Special Publication 812: *Criteria for the Operation of Federally-Owned Secondary Calibration Laboratories (Ionizing Radiation);* NIST Handbook 150: *NVLAP Procedures and General Requirements;* and ISO Guide 25: *General Requirements for the Competence of Calibration and Testing Laboratories.*

ULTRASOUND

Hydrophone Calibration at Low Frequencies

Key words: ultrasound, exposimetry, hydrophone

OST engineers have shown that the low-frequency response of hydrophones is important for accurate ultrasound pulse measurements. These measurements are needed to calculate the peak rarefactional pressure, an important quantity for assessing the likelihood of cavitation onset, as well as the Mechanical Index, a related quantity displayed on diagnostic ultrasound equipment that gives an indication of the potential for mechanical damage to exposed tissues. However, frequency response data below 1-2 MHz typically are not available for commercial hydrophones designed for measurements in medical ultrasound fields. Therefore, OST engineers measured the low-frequency response of a number of miniature hydrophones used in biomedical ultrasonics.

Broadband pressure pulses were used in these measurements using a technique developed in OST. A chief advantage of the measurement technique was the ability to obtain broadband calibration data in a single measurement, as opposed to more time consuming single-frequency techniques. Also, because of the plane-wave nature of the calibration pulses, there was no need for precise source-hydrophone positioning or corrections for hydrophone spatial averaging. However, sensitivity was poor since the source transducer was neither focused or operated in a resonant mode; so hydrophone signal amplification and waveform averaging were necessary.

Eleven hydrophones were included in the study. Six were needle-type hydrophones from four commercial sources, and three were spot-poled membrane hydrophones from three commercial sources. Two other spot-poled membrane hydrophones made in the OST ultrasound laboratory also were included. For the spot-poled membrane hydrophone sensitivities, no significant deviation from a flat, uniform response was seen. The needle-type hydrophones, on the other hand, all displayed a roll-off in low frequency response. The roll-off frequency was affected by the size and shape of the needle tip, a result in qualitative agreement with a diffraction-based calculation of the pressure on the end of a needle-type hydrophone when modeled as a rigid, cylindrical rod.

Although needle-type hydrophones have advantages in certain measurement situations, the response roll-off observed at low frequencies calls these devices into question when accurate knowledge of the transmitted pressure pulse is needed. This is particularly true

in waveforms displaying significant finite amplitude distortion, a common occurrence when biomedical ultrasound fields are measured in water as required in current standards. The results of this study are affecting both Center 510(k) guidance and national and international ultrasound measurement standards.

Accuracy of Doppler Ultrasound

Key words: Doppler, ultrasound, blood velocity

Color Doppler diagnostic ultrasound provides a two-dimensional map where the velocity magnitude at each point in the image is encoded in color. This mode is primarily used in a qualitative fashion to provide an overall view of the blood flow (as in the cardiac chambers). For quantitative measurements, the machine is typically switched to pulsed Doppler mode, where only the velocity at a single point is displayed, sacrificing the two-dimensional imaging capability. However, there are many examples in the literature using color Doppler quantitatively, e.g., to measure regurgitation in prosthetic heart valves. If the accuracy of color Doppler is affirmed, then quantitative uses such as this may become more common.

Hundreds of thousands of ultrasound exams are performed each year. The important clinical parameter determined by Doppler is blood velocity; yet there are no good quality assurance tests for the manufacturer or for the hospital physicist to determine whether the results from any machine are accurate. OST scientists have developed a promising new technique to meet this problem. The test object is called the torus phantom and was described briefly in past reports. The design of the phantom has been finalized, to remove errors due to transducer placement. Flow visualization in a transparent torus as well as numerical computations have confirmed that the phantom provides a stable, constant flow velocity over a large area of fluid.

Extensive tests of color Doppler B-mode in a commercial ultrasound system were performed, using a transducer intended for imaging arteries. Results of the experiments showed statistically significant effects on color Doppler accuracy of two instrument settings: the pulse repetition frequency (PRF) and wall filter (WF). A significant complex interaction between these two settings was also observed. The effect on accuracy was also significantly dependent on the velocity being measured. Overall, the particular transducer used in these tests gave velocities that were approximately 15% low. Preliminary tests, however, showed that the machine's other transducers were more accurate. No significant effect of the machine's power setting or gain was found, provided that the settings were adjusted so that a clear image was produced. Error analysis demonstrated that the torus phantom provides fluid velocities accurate to within a few percentage points. This is well within the accuracy needed to help manufacturers and clinicians transform color Doppler from a purely qualitative procedure into a viable method for making quantitative measurements.

Ultrasound Bone Densitometry

Key words: backscatter, bone density

A grant from the FDA Office of Women’s Health for a study titled: Development and Validation of Ultrasonic Backscatter Measurement for Bone Density Assessment

($62,000 for 2 years), was awarded April 1998 to develop a novel ultrasonic bone densitometric system to be tested on 100 normal female volunteers. The new system is based on ultrasonic backscatter rather than attenuation and speed of sound as other systems. A prototype system was designed and built. Preliminary tests on tissue-mimicking phantom materials were conducted. CDRH /Research Involving Human Subjects Committee (RIHSC) approval was obtained for the clinical study.

The United States Army previously awarded a grant in March 1998 for a joint CDRH-CFSAN study: A Dietary Strategy to Maximize Bone Mass in United States Naval Academy Midshipmen ($775,000 for 2 years). The main focus of this study is to use bone densitometry to monitor the effects of dietary supplements on bone growth in young healthy adults. FDA/RHISC approval was obtained for this study.

Appendix A - OST Publications

October 1, 1997 – September 30, 1998

Journal Articles

Bassen HI, Moore HJ, Ruggera PS. Cellular phone interference testing of implantable cardiac defibrillators *in vitro*. *PACE* **21**:1709-1715, 1998.

Bassen HI. Radiofrequency interference with medical devices – a technical information statement. *IEEE Engineering in Medicine and Biology Magazine* **17(3)**:111-114, 1998.

Bassen HI. Electric field probes for cellular phone dosimetry. Proceedings of the 19th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, pp. 2942-2945, October 30 – November 2, 1997.

Beard B, Stewart JR, Fischell TA. A system for postoperative visualization and analysis of left ventricular pressure-volume loops. *Computers in Biology and Medicine* **28(1**) 1998.

Bockstahler LE, Sagripanti JL. Optimizing PCR for detection for an RNA virus. FDA Laboratory Information Bulletin 13:1-11 (FDA guideline document #4094), 1997.

Boone JM., Fewell TR, Jennings RJ. Molybdenum, rhodium, and tungsten anode spectral models using interpolating polynomials with application to mammography. *Med. Phys.* **24 (12)**:1863-1874, 1997.

Brown SL, Langone JJ, Brinton LA. Silicone breast implants and autoimmune disease. *Journal of the Medical American Women's Association* **53(1):**21-24, 1998.

Carey RF, Lytle CD. More stringent testing necessary for medical devices? *Rubber Asia* **11(6)**:69-70, 1997.

Cyr WH. CDRH evaluation of UV-emitting sunlamp products. CRCPD Publication 98-5:262-268, 1998.

Demian HW, McDormott K. Regulatory perspective on characterization and testing of orthopedic bone cements. *Biomaterials* **19:**1607-1618, 1998.

Durkin AJ, Ediger MN, Pettit GH. Raman spectroscopy for quantification of polydimethylsiloxane concentration in turbid samples. *Lasers in Medical Science* **13(1)**:32-41, 1998.

Durkin AJ, Matchette LS, Ediger MN. Determination of silicone concentrations from raman spectra using the method of partial least squares (PLS). *Biomedical Optical Spectroscopy and Diagnostics/Therapeutic Laser Applications* **22**:164-167, 1998.

Ediger MN, Durkin AJ. Lasers in healthcare: focus on corneal refractive surgery. *Optics and Photonics News* **8(11)**:18-22, November, 1997.

Finder CA, Kisielewski RW, Kedas AM. Residual metal shaving and fragments associated with large-core biopsy needles: a follow-up. *Radiology* **208(3):**833-834, 1998.

Gaylor DW, Axelrad JA, Brown RP, Cavagnaro JA, Cyr WH, Hulebak KL, Lorentzen RJ, Miller MA, Muligan LT, Schwetz BA. Health risk assessment practices in the U.S. Food and Drug Administration. *Regulatory Toxicology and Pharmacology* **26**:307-321, 1997.

Hughes-Dillon K, Schroeder LW. Stress cracking of polyurethanes by absorbed steroids. *Polymer Degradation and Stability* **60:**11-20, 1998.

Kimmelman E, Higson G, Hoyt M, Marlowe DE, Hilz E, Vukmanovich A, Barth D. Regulatory harmonization and standards development: opportunities for cooperation. *Biomedical Instrumentation and Technology,* AAMI **31(5)**, September/October 1997.

Krauthamer V, Jones JL. Effects of biphasic electric shocks on calcium changes in cultured cardiac myocytes. *In Vitro and Molecular Toxicology* **11(3)**:221-228, 1998.

Liesi P, Wright JM, Krauthamer V. BAPTA-AM and ethanol protect cerebellar granule neurons from the destructive effect of the weaver gene. *Journal of Neuroscience Research* **48**:571-579, 1997.

Lopez H, Harris KM. Ultrasound interactions with free silicone in a tissue-mimicking phantom. *Journal of Ultrasound In Medicine* **17**:163-170, March 1998.

Lopez H. How to interpret the ultrasound output display standard for higher acoustic output diagnostic ultrasound devices. *Journal of Ultrasound in Medicine* **17(8)**:535-538, August 1998.

Luu MD, Hutter JC, Bushar H. A physiologically based pharmacokinetic model for 2,4 toluenediamine leached for polyurethane foam-covered breast implants. *Environmental Health Perspectives* **106(7):**393-400, 1998.

Lytle CD, Routson LB, Duff JE, Fleharty B, Bidinger RL, Cyr WH. A sensitive method to evaluate condoms as virus barriers. *J Assoc Offic Analyt Chem, Intl* **8:**319-324, 1997.

Malinauskas RA, Sarraf P, Barber K, Truskey GA. Association between secondary flow in models of the aorto-celiac junction and subendothelial macrophages in the normal rabbit. *Atherosclerosis* **140**:121-134, 1998.

Malinauskas RA. Plasma hemoglobin measurement techniques for the *in vitro* evaluation of blood damage caused by medical devices. *Artificial Organs* **21**:1255-1267, 1997.

Marlowe DE, Phillips P. FDA recognition of consensus standards in the premarket notification process. *AAMI Biomedical Instrumentation and Technology* pp. 301-303, May/June 1998.

Mehta RI, Lytle CD, Thomas DP, Myers MR. The cause of cessation of viral passage through holes in latex condoms. *Journal of Rubber Research* **1(1):**1-13, 1998.

Merritt K, Gaind A, Anderson JM. Detection of bacterial adherence on biomedical polymers. *Journal of Biomedical Research* 39:415-422, 1998.

Miller SA, Hamilton SL, Wester UG, Cyr WH. An analysis of UVA emissions from sunlamps and the potential importance for melanoma. *Photochemistry and Photobiology* **68(1)**:63-70, 1998.

Mueller EP, Regnault WF. Replacement heart valves and performance standards. *Journal of Heart Valve Disease* 7:125-129, March 1998.

Myers MR, Malinauskas RA. Effect of orifice-area reduction on flow characteristics during injection through spinal needles. *Anaesthesia* **53**:151-156, 1998.

Myers MR, Kerschen EJ. Influence of camber on sound generation by airfoils interacting with high-frequency gusts. *Journal of Fluid Mechanics* **353**:221-259, December 1997.

Norrby NE, Grossman LW, Geraghty EP, et al. Determining the imaging quality of intraocular lenses. *J Cataract Refract Surgery* **24(5)**:703-714, 1998.

Owen RD. MYC mRNA abundance is unchanged in subcultures of HL60 cells exposed to power-line frequency magnetic fields. *Radiation Research* **150**:23-30, 1998.

Page BFJ, Cyr WH. A guide to AAMI's TIR for EtO-sterilized medical devices. *Medical Device and Diagnostic Industry*, pp.73-78, February 1998.

Park E, Condrate RA, Hoelzer DT, Fischman GS. Interfacial characterization of plasma-spray coated calcium phosphate on Ti-6A1-4V. Journal of Materials Science **9**:643-649, 1998.
Pierdominici Jr. VJ, Doucette JM, Coyne, Cyr WH, Thomas DP, Lytle CD. Ability of quality assurance tests to detect punctured latex condoms with potential for virus penetration. *Journal of Testing and Evaluation* **26(1):**10-14, 1998.

Placko HE, Brown SA, Payer JH. Effects of microstructure on the corrosion behavior of CoCr porous coatings on orthopedic implants. *J Biomedical Materials Research* **39**:292-299, 1998.

Pritchard WF, Carey RF. U.S. Food and Drug Administration and regulation of medical devices in radiology. *Radiology* **205(1)**:27-36, 1997.

Rosen LA, Barber I, Lyle DB. A 0.5 G, 60-Hz magnetic field suppresses melatonin production in pinealocytes. *Bioelectromagnetics* **19**:123-127, 1998.

Rupal I, Mehta C, Lytle CD, Thomas DP, Myers MR. Cause of cessation of viral passage through artificially induced holes in latex condoms. *Journal of Rubber Research* **1(1):**1-13, 1998.

Sagripanti J-L, Bonifacino A. Effect of salt and serum on the sporicidal activity of liquid disinfectants. *J. AOAC International*, **80(6):**1198-1207, 1997.

Sagripanti J-L, Eklund CA, Trost PA, Jinneman KC, Abeyta C, Kaysner CA, Hill WE. Comparative sensitivity of thirteen species of pathogenic bacteria to seven chemical germicides. *American Journal of Infection Control* **25**:335-339, 1997.

Sagripanti JL, Routson LB, Bonifacino A, Lytle CD. Mechanism of copper-mediated inactivation of herpes simplex virus. *Antimicrobial Agents and Chemotherapy* **41**:812-817, 1997.

Shope TB. Medical physics and the "Year 2000 date problem." *American Association of Physicists in Medicine Newsletter*. May/June 1998, pp. 11-12.

Skopec M. Hearing aid electromagnetic interference from digital wireless telephones. *IEEE Transactions on Rehabilitation Engineering* **6(2)**:235-239, June 1998.

Stern RS, Mills DK, Krell K, Zmudzka BZ, Beer JZ. HIV-positive patients differ from HIV-negative patients in indications for and type of UV therapy used. *J. Am. Acad. Dermatol.* **39**:48-55, 1998.

Stewart SFC. Aliasing-tolerant color Doppler quantification of regurgitant jets. *Ultrasound in Medicine and Biology* **24(6)**:881-898, 1998.

Turcotte J, Witters D. A practical technique for assessing electromagnetic interference in the clinical setting: ad hoc testing. *Biomedical Instrumentation & Technology* **32(3)**:241-252, 1998.

Wear KA, Myers KJ, Rajan SS, Grossman LW. Constrained reconstruction applied to 2D chemical shift imaging. *IEEE Transactions in Medical Imaging.* **16(5)**:591-597, 1997.

Wear KA, Garra BS. Assessment of bone density using ultrasonic backscatter. *Ultrasound in Medicine and Biology* **24(5)**:689-695, 1998.

Woods TO, Berghaus DG, and Peacock HB. Interparticle movement and the mechanical behavior of extruded powder aluminum at elevated temperature. *Experimental Mechanics* **38(2)**:110-115, June 1998.

Zmudzka BZ, Beer JZ. Ultraviolet therapy and patients with HIV infection. *Archives of Dermatology* **134(8)**:1025-1026, 1998.

Books and Chapters in Books

Hellman KB, Knight E, Durfor C. Product applications and regulatory issues. In: Frontiers in Tissue Engineering, C.W. Patrick, Jr., A.G. Mikos, and J.L. McIntire, eds. Pergamon Press, Elsevier Science, Inc., pp. 341-366, New York, 1998.

McCombie WR, Wilson R, Chen L, Gibbs R,..., Sagripanti J-L. Complete sequences of Homo sapiens ccr2b, ccr2a, ccr5 and ccr6 genes, and lacoferrin gene (143068 bp). In: GeneBank Database, accession # U95626, 1997.

Merritt K. Immune Response. In: Handbook of Biomaterial Properties. J Black and G Hastings (Eds.), Chapman & Hall, London. Part III, Chapter 4, pp. 513-525, 1998.

Sagripanti J-L. DNA damage mediated by metal ions. In: Interrelations between Free Radicals and Metal Ions in Life Processes. Metal Ions in Biological Systems Series, Vol. 36. A.Sigel and H. Sigel (Eds.) Marcel Dekker, New York, 1998.

Wilson SH, Singhal RK, Zmudzka BZ. Studies of DNA polymerases in replication-based repeat expansion. In: Genetic Instabilities and Hereditary Neurological Diseases, RD Wells and ST Warren, (Eds), Academic Press, San Diego, CA, pp. 693-698, 1998.

Proceedings, Abstracts, Letters, Book Reviews, etc.

Almara A, Bockstahler LE, and Sagripanti JL. Comparative detection of Junin virus by polymerase chain reaction and probe hybridization. Argentina Society of Clinical Research, Buenos Aires, Argentina, October 15, 1997 (abstract).

Beer JZ. Tanning devices: concerns and options for action. FDA Photosciences Workshop, Gaithersburg MD, abstract 10:25, 1997.

Beer JZ, Godar DE, Zmudzka BZ. The importance of UV action spectra. FDA Photosciences Workshop, Gaithersburg MD, abstract 10:10, 1997.

Beer JZ, Kornhauser A, Osterberg RE, Vostal JG. The FDA Photosciences Network (Photomedicine-Photobiology-Photochemistry-Photophysics). FDA Forum on Regulatory Sciences, Washington, DC, abstract O-1, p.147, 1997.

Beer JZ, Zmudzka BZ. Gene activation by UV (and drugs): effective exposures in experiment and real life. *Photochem. Photobiol.* **67(S)**, 50S, 1998.

Bockstahler LE. Development of written voluntary consensus standards for polymerase chain reaction. FDA Forum on Regulatory Sciences, Bethesda, MD, December 8-9, 1997 (abstract).

Brown DG, Anderson MP, Myers KJ. Neural-network decision functions for a limited-view reconstruction task. Proceedings of the SPIE (Conference on Image Processing*)* **3338**:355-362, 1998.

Chan HP, Sahiner B, Wagner RF, Petrick N. Effects of sample size on classifier design for computer-aided diagnosis. Proceedings of the SPIE (Conference on Image Processing*)* **3338**:845-858, 1998.

Chen ET, Fabrication and characterization of a novel qamperometric biomimetic enzyme sensor. 215th ACS National Meeting, Books of Abstracts, COLL-308, American Chemical Society, 1998.

Chen ET, Schroeder LW, Luu MD. Error analysis for three commonly used clinical methods for blood glucose monitoring at two accredited clinical hospital laboratories. Clinical Chemistry, **44(6)**, 1998.

Chwirut DJ, Oktay HS, Ryan T. Nitinol interventional cardiology devices – FDA's perspective. In SMST-97: Proceedings of the Second International Conference on Shape Memory and Superelastic Technologies, Pelton A, Hodgson D, Russell S, and Duering T (Eds.), SMST, Santa Clara, CA, 1997.

Cress LW, Owen RD, Desta AB. Ornitihine decarboxylase activity following exposure to 60-Hz magnetic fields (abstract). Proceedings of the Annual Review of Research of Biological Effects of Electric and Magnetic Fields form the Generation, Delivery, and Use of Electricity, San Diego, CA, p. 57, 1997.

Cress LW, Owen RD, Desta AB. Ornitihine decarboxylase activity following exposure to 60-Hz magnetic fields (abstract). Proceedings of the FDA Science Forum on Regulatory Sciences, Washington, DC, p. 117, 1997.

Cress LW, Owen RD, Desta AB. Ornitihine decarboxylase activity in developing chick embryos after exposure to 60-Hz magnetic fields (abstract). Proceedings of the Annual Review of Research of Biological Effects of Electric and Magnetic Fields form the Generation, Delivery, and Use of Electricity, Tucson, AZ, p. 66, 1998.

Fisher BR, Papaconstantinou A, and Goering PL. Mercuric chloride induces regional expression of heat shock proteins in rat kidney. *Toxicol. Sci*. Supplement **42**:377, 1998.

Frick C, Tomazic-Jezic V, Umbreit T, and Merritt K. *In vivo* effects of polymethylmethacrylate (PMMA) and polystyrene (PS) particles on splenic and peritoneal exudate cells (PEC). Society for Leukocyte Biology, Supplement, abstract 17, Baltimore, MD, 1997.

Gagne RM, Wagner RF. Prewhitening matched filter: practical implementation, SNR estimation and bias reduction. Proceedings of the SPIE (Conference on Physics of Medical Imaging*)* **3336**:231-242, 1998.

Godar DE, Lucas AD. Spectral dependence of UV-induced immediate and delayed apoptosis: the role of membrane damage. FDA Forum on Regulatory Sciences, Bethesda, MD, abstract G8, p. 86, 1997.

Goering PL, Morgan DL, Ali SF. Effect of mercury vapor inhalation on reactive oxygen species and antioxidant enzymes in rat brain and kidney. *Toxicol. Sci*. Supplement **42**:193, 1998.

Goering PL, Waalkes MP. The enigma of arsenic carcinogenesis: role of metabolism. *Toxicol. Sci*. Supplement **42**:352, 1998.

Gonzalez G, Nueland CY, Zmudzka BZ. UVB-irradiated donor blood transfusions in renal transplantation: the CDRH perspective. FDA Photosciences Workshop, Gaithersburg MD, abstract 2:40, 1997.

Gutierrez A, Sagripanti JL. Studies of the interaction of copper ions with DNA by nuclear magnetic resonance. FDA Forum on Regulatory Sciences, Bethesda, MD. 1997 (abstract).

Harris GR, Gammell PM. Effects of diffraction on the sensitivity of needle-type ultrasonic receivers. Proceedings: 16th International Congress on Acoustics and 135th Meeting of the Acoustical Society of America, pp. 2311-2312, June 20-26, 1998.

Heaton HT, Cerra F, Zaini MR, McCune CG, Stauffer CL, Furfine CS, Fewell TR. Calibrating mammography instruments: methods and issues. Proceedings of the 29th Annual Conference of Radiation Control Program Directors, CRCPD Publication 97-3, 109-125 (1997).

Hellman KB. Tissue engineering: advances in applications. BioConferences International Sixth Annual Congress on Women's Health From Bench to Bedside, June 1998 (abstract).

Hellman KB. TSE risks: meeting the challenge (opening and closing remarks). Transcript, Joint Institute for Food Safety and Applied Nutrition (JIFSAN) Workshop on TSE Risks in Relation to Source Materials, Processing, and End-Product Use, June 1998 (abstract).

Hellman KB. Human dura mater issue: update and FDA-proposed course of action. Transcript, Public Meeting of FDA Transmissible Spongiform Encephalopathies Advisory Committee, April 15-16, 1998 (abstract).

Hellman KB. FDA regulatory response to public health issues of TSE/BSE. American Occupational Health Care Conference, Annual Meeting, American College of Occupational and Environmental Medicine, April 1998 (abstract).

Hitchins VM, Chapekar MS, Zaremba TG, Merritt K. Induction of nitric oxide, TNF-alpha, IL-4, and IL-6 by LPS in combination with silicon dioxide (SiO_2) and amorphous silica in RAW 264.7 murine macrophages. FDA Forum on Regulatory Sciences, Bethesda, MD, abstract G11, p. 88, Dec 1997.

Hitchins VM, Merritt K. Decontaminating particles exposed to bacterial endotoxin (LPS). Transactions of the Society for Biomaterials, Volume XXI, p. 311, 1998.

Hoin FA, Landry RJ, Sliney DH. Determination of pulsed lamp source size. International Symposium on Measurements of Optical Radiation Hazards, p 46, September 1-3, 1998.

Kaplan DS , Picciolo GL., Moore MA, Kowolik MJ. Evaluation of respiratory burst of human leukocytes to pyrolytic carbon used in biomedical applications. Society for Leukocyte Biology 32nd National Meeting in Baltimore, MD. *J. Leukocyte Biol*., Supp 1997. December 1997.

Kimmelman E, Higson G. Hoyt M, Marlowe D, Hilz E, Vukmanovich A, Barth D. Regulatory harmonization and standards development: opportunities for cooperation. Biomedical Instrumentation and Technology, AAMI, 31(5), September/October 1997.

Krauthamer V. Intracellular calcium dynamics in cultured embryonic heart cells exposed to electric shocks. Proceedings of the American Heart Association Scientific Conference on Ventricular Fibrillation: a pediatric problem, pp. 3, Seattle, WA, July 9-11, 1998.

Landry RJ, Levin RE, Bergman RS. CIE photobiological lamp safety standards. International Symposium on Measurements of Optical Radiation Hazards, p 26, September 2, 1998.

Levin RE, Landry RJ. ANSI/IESNA photobiological lamp safety standards. International Symposium on Measurements of Optical Radiation Hazards, p 26, September 2, 1998.

Lucas AD, Li QX, Seiber JN. Update on the integration of immunochemical methods with other analytical techniques. *Inside Laboratory Management,* March 1998.

Lyle DB, Langone JJ. The immunotoxicity electronic network. FDA Forum on Regulatory Sciences, Bethesda, Maryland, December 8-9, 1997 (abstract).

Malinauskas RA. Plasma hemoglobin assays for *in vitro* hemolysis testing. Proceedings of the 1997 FDA Forum on Regulatory Sciences, Bethesda, MD, (Abstract A19) December 1997.

Matchette SL, Durkin AJ, Miller SA, Zmudzka BZ, Beer JZ, Virmani M, Pollard CM. Interaction of UV radiation with mucosal tissue: comparison with skin. FDA Photosciences Workshop, Gaithersburg MD, abstract 11:10, 1997.

McCombie WR, Wilson R, Chen L, Gibbs R, Sagripanti JL. Complete sequences of Homo sapiens ccr2b, ccr2a, and ccr6 genes and lacoferrin gene (143068 bp). GeneBank Database, accession #U95626, 1997.

McCormick DL, McDonald LJ, Gauger JR, Johnson TR, Cress LW, Owen RD, Desta AB, Savage RA, Lotz WG, Zhu H, Mandeville R. Ornitihine decarboxylase activity in rat tissues exposed *in vivo* to complex power frequency magnetic field metrics: an interlaboratory program (abstract). Proceedings of the Annual Review of Research of Biological Effects of Electric and

Magnetic Fields form the Generation, Delivery, and Use of Electricity, San Diego, CA, pp. 55-56, 1997.

McCormick DL, McDonald LJ, Loberg LI, Gauger JR, Mandeville R, Owen RD, Cress LW, Desta AB, Lotz WG, Savage RE, Zhu H. Ornitihine decarboxylase activity in tissues from rats exposed to complex magnetic field metrics (abstract). Proceedings of the Bioelectromagnetics Society 20th Annual Meeting, St. Pete Beach, FL, p. 177, 1998.

McDonald LJ, Loberg LI, Mandeville R, Owen RD, Cress LW, Desta AB, Lotz WG, Savage RE, Zhu H, Gauger JR, McCormick DL. Ornithine decarboxylase activity in tissues from rats exposed to pure 60-Hz magnetic fields and magnetic field harmonics (abstract). Proceedings of the Bioelectromagnetics Society 20th Annual Meeting, St. Pete Beach, FL, p.127, 1998.

Merritt K, Hitchins VM, Brown SA, Woods TO. Cleaning biological debris from materials and effects of the cleaning process on material properties. Transactions of the Society for Biomaterials, Volume XXI, p. 372, 1998.

Merritt K, Hitchins VM, Brown SA. Materials consideration in reusable devices. AAMI & FDA, Reprocessing Medical Devices, Dallas TX, November 1997.

Merritt K, Hitchins VM, Brown SA. Materials considerations in reusable devices. FDA Forum on Regulatory Sciences, Washington, D.C., abstract C8, p. 59, December 1997.

Merritt K. Infection. In: Biological Response to Orthopedic Implants, Johns Hopkins Medical Institutions, May 1998.

Mia RS, Loew M, Wear KA, Wagner RF, Myers KJ. Quantitative ultrasound tissue characterization using texture, spectral, and cepstral features. Proceedings of the SPIE (Conference on Image Processing) **3338**:211-219, 1998.

Mia RS, Loew MH, Wear KA, Wagner RF, Garra BS. The use of intra-patient variability of extracted parameters to discriminate hepatitis in the liver. Proceedings of the 23rd International Symposium on Ultrasonic Imaging and Tissue Characterization, Arlington, VA, p. 12, May 27-29, 1998.

Miller SA, Sayre RM, Cyr WH. Comparison of UV emissions from sunlamps and from solar exposure through sunscreens: the potential importance for melanoma. American Society for Photobiology, **v67**, p2S, July 1998.

Morehouse CA, Owen RD. Exposure to a 50 μT, 60-Hz magnetic field does not induce MYC in Daudi Cells (abstract). Proceedings of the Annual Review of Research of Biological Effects of Electric and Magnetic Fields form the Generation, Delivery, and Use of Electricity, San Diego, CA, pp. 56-57, 1997.

Morehouse CA, Owen RD. Exposure to a 50 μT, 60-Hz magnetic field does not induce MYC in Daudi Cells (abstract). Proceedings of the FDA Forum on Regulatory Sciences, Washington, DC, p. 117, 1997.

Morehouse CA, Owen RD. Exposure to electric and magnetic fields does not induce hsp70 in HL60 cells (abstract). Proceedings of the Annual Review of Research of Biological Effects of Electric and Magnetic Fields form the Generation, Delivery, and Use of Electricity, Tucson, AZ, p.44, 1998.

Neale AR, Merritt K, Brown SA. Evaluation of a dye penetration test for package integrity. FDA Forum on Regulatory Sciences, Bethesda, MD, abstract B13, p. 45, December 1997.

Nueland CY, Gonzalez G, Zmudzka BZ. UVR^{R} Photopheresis system: background and CDRH issues. FDA Photosciences Workshop, Gaithersburg MD, abstract 2:00, 1997.

Papaconstantinou AD, Brown KM, Lappas NT, Fisher BR, Umbreit TH. Estrogenicity and heat shock proteins: Bisphenol A. *Toxicol. Sci*. **42(1):**175, Suppl., abstract 865, 1998.

Papaconstantinou AD, Brown KM, Umbreit TH, Fisher BR. Bisphenol A: *In vivo* estrogenic activity. FDA Forum on Regulatory Sciences, Bethesda, MD, abstract B14, p. 45, 1997.

Picciolo GL, Hellman KB, Tesk J, Valentini R, Coury A, Johnson P. "Living" standards. Biomaterials Forum **20(1)**:17-18, January-February 1998.

Picciolo GL, Hellman KB, Johnson P. The standards development process for tissue-engineered medical products. IBC USA Conferences, Advances in Tissue Engineering, June 1998 (abstract).

Sagripanti JL, Merritt K, Hilbert S, Hitchins V, and Matchette S. Current issues on liquid disinfection and sterilization of medical devices. FDA Internal Policy Document, April 1997.

Schwetz BA, Sheehan D, Brand D, Bolger M, Stromberg K, Leighton J, Umbreit T, McNerney ME, Golden L, D'Hoostelaere L, Homire S, Wilcox N. FDA Endocrine Disrupter Committee. FDA Forum on Regulatory Sciences, Bethesda, MD, abstract O6, p. 149, 1997.

Tomazic-Jezic VJ, Truscott W. Specificity of rabbit sera immunized with either ammoniated (AL) or nonammoniated (NAL) latex extracts. FDA Forum on Regulatory Sciences, Bethesda, MD, abstract B24, p. 50, 1997.

Umbreit TH, Fisher BR, Papaconstantinou AD, and Brown KM. Preliminary development of an in vivo assay for estrogenicity. FDA Forum on Regulatory Sciences, Bethesda, MD, abstract B26, p. 51, 1997.

Umbreit TH, Tomazic-Jezic V, Frick C , Merritt K. *In vivo* effects of polymethylmethacrylate (PMMA) and polystyrene (PS) particles on splenic and peritoneal exudate cells. FDA Forum on Regulatory Sciences, Bethesda, MD, abstract B25, p. 51, 1997.

Umbreit TH, Tomazic-Jezic VJ, Merritt K. Polystyrene (PS) and polymethylmethacrylate (PMMA) particles in the mouse: effect of particle size and composition on deposition following IP injection. *Toxicologist (Fund. Appl. Toxicol.),* **36(1):**197, abstract 1003, 1997.

Wagner RF., Chan HP, Mossoba JT, Sahiner B, Petrick N. Components of variance in ROC analysis of CADx classifier performance. Proceedings of the SPIE (Conference on Image Processing) **3338**:859-876, 1998.

Wagner RF, Chan HP, Mossoba JT, Sahiner B, Petrick N. Uncertainties in ROC analysis of tissue classifier performance. Part 1: bias of classifiers. Proceedings of the 23rd International Symposium on Ultrasonic Imaging and Tissue Characterization, Arlington, VA, p. 48, May 27-29, 1998.

Wagner RF, Chan HP, Mossoba JT, Sahiner B, Petrick N. Uncertainties in ROC analysis of tissue classifier performance. Part 2: bias of classifiers. Proceedings of the 23rd International Symposium on Ultrasonic Imaging and Tissue Characterization, Arlington, VA, p. 48, May 27-29, 1998.

Waynant RW, Chenault VM. Overview of noninvasive fluid glucose measurement using optical techniques to maintain glucose control in diabetes mellitus. IEEE LEOS Newsletter, pp. 3-6, April 1998.

Waynant RW, Chenault VM. Use of low-level laser therapy to accelerate wound healing in an animal model of diabetes: overview of the model and preliminary/future studies. World Association for Laser Therapy, pp. 112-113, September 5, 1998.

Wear KA., Garra BS. Assessment of bone density using broadband ultrasonic backscatter. Proceedings of the 22nd International Symposium on Ultrasonic Imaging Tissue Characterization, 48, 1997.

Wear KA, Wagner RF. Uncertainties in estimates of low-contrast sensitivity of medical ultrasonic imaging systems. Proceedings of the 23rd International Symposium on Ultrasonic Imaging and Tissue Characterization, Arlington, VA, p.48, May 27-29, 1998.

Zmudzka BZ, Beer JZ. Analysis of risks from HIV activation and immune modulation in UVB and PUVA therapies. *Photochem. Photobiol.* **67(S)**, 17S, 1998.

Zmudzka BZ, Adams ML, Beer JZ, Bethke FR, Cruz PD, Lightfoote MM, Shearer GM. Lymphokine profiles in psoriasis patients treated with UVB therapy. FDA Forum on Regulatory Sciences, Washington, DC, abstract I-24, 116, 1997.

Zmudzka BZ, Beer JZ, Nueland CY, Gonzalez G. UV-induced suppression of the immune system: regulatory and laboratory aspects. FDA Photosciences Workshop, Gaithersburg MD, abstract 1:55, 1997.

Office of Science and Technology Internal Reports

Chen ET. Analysis of the trends from 125 granted biosensor research proposals nation-wide for the FDA microarray DNA workshop. DMMS Report #98-09, May 15, 1998.

Chwirut DJ. Laboratory evaluation of the RespAide™ resuscitation filter. DMMS Report #98-07, July 1998.

Dubill PM. Interlaboratory study on puncture resistance testing of sharps containers. DMMS Report #98-01, January 1998.

Hilbert SL. Allograft heart valves: the role of apoptosis-mediated cell loss. DMMS Report #98-06, 1998.

Hilbert SL. Allograft heart valves: morphologic, biomechanical and explant pathologic studies. DMMS Report #98-08, 1998.

FY 98 ORA Research Projects/Winchester Engineering And Analytical Center (WEAC)

Boivin W, Boyd S, Coletta S, Harris C, Neunaber L. Validation of the American National Standards Institute (ANSI) Ad Hoc Test Method for Estimating Radiated Electro-Magnetic Immunity of Medical Devices to Specific Radio-Frequency (RF) Transmitters.

Boyd S, Boivin W, Coletta J, Harris C, Neunaber L. Development of methods to characterize the electromagnetic fields in non-hospital healthcare environments.

Chaput M. Development of a cell culture assay test for viability and infectivity of *Cyclospora cayetanesis.*

Clavet C, Regan P. Development of HSV-1 and HSV-2 quality control serum panel.

DiNovo J, Landry R. Development of a test method for determining the accuracy of infrared (ir) ear thermometers.

Galevi E. Determining the regulatory suitability of standard electroacoustical testing and validation of technical performance of hearing aids.

Hamilton S, Miller S. Risk assessment of radiation hazard from operating (surgical) microscope light emission.

Neunaber L, Boivin W, Boyd S, Mailhot S, Pierdominici V Jr. Development and validation of a universal water leak test method for barrier contraceptives

Regan P, Wilson J, Clavet C. Development of a rapid molecular technique to detect viable *Cryptosporidium parvum* following germicidal treatment.

Regan P, Clavet C. Establishment of a standardized method to determine the analytical sensitivity of herpes simplex virus *in-vitro* diagnostic test kits.

Rodriguez A, To T. Evaluation of the effects of organic soils in testing disinfectants on model viruses and prototype carriers.

Rodriguez A, To T, Leonard I. Evaluation of a complex spore carrier for use in testing the sporicidal activity of disinfectants.

Wilson J. Evaluation of liquid germicidal inactivation rates for *Cryptosporidium parvum* oocysts.

Appendix B – OST Presentations

October 1, 1997 – September 30, 1998

Beard B. Cardiovascular research at the FDA. The Center for Emerging Cardiovascular Technologies at Duke University National Science Foundation, Durham, NC, October 1997.

Beer JZ (speaker). Tanning devices: concerns and options for action. FDA Photosciences Workshop, Gaithersburg MD, abstract 10:25, 1997.

Beer JZ (speaker), Godar DE, Zmudzka BZ. The importance of UV action spectra. FDA Photosciences Workshop, Gaithersburg MD, abstract 10:10, 1997.

Beer JZ (speaker), Kornhauser A, Osterberg RE, Vostal JG. The FDA Photosciences Network (Photomedicine-Photobiology-Photochemistry-Photophysics). FDA Forum on Regulatory Sciences, Washington, DC, abstract O-1, p.147, 1997.

Beer JZ (speaker), Zmudzka BZ. Gene activation by UV (and drugs): effective exposures in experiment and real life. *Photochem. Photobiol.* **67(S)**, 50S, 1998.

Bockstahler LE. PCR inhibitors and TB detection. Invited seminar at 1998 World TB Day CBER-CDER-CDRH Workshop, Gaithersburg, MD, March 24, 1998.

Bockstahler LE. Screening medications for their ability to inhibit PCR detection of mycobacterium tuberculosis. Invited seminar at Division of Microbiology, National Center for Toxicological Research, FDA, Jefferson, AK, May 13, 1998.

Bockstahler LE. Screening medications for their ability to inhibit PCR detection of mycobacterium tuberculosis. Invited seminar at Department of Microbiology, University of Miami, Miami, FL, May 15, 1998.

Brown DG. Responsible monitoring of clinical software systems: the FDA perspective. American Medical Informatics Association Annual Meeting, Orlando, FL, November 1997.

Brown RP. Paradigm for the biological evaluation of medical devices. Biomedical Focus ' 98. Minneapolis, MN, July 22, 1998.

Chen ET, Pardue HL. Quantification of o-nitrophenyl acetate by using novel ampermetric biomimetic enzyme sensors. FDA Forum on Regulatory Sciences, Bethesda, MD, Abstract B6, **41**, December 1997.

Chen ET. Is the system error negligible for CDC's blood glucose reference method? FDA Forum on Regulatory Sciences, Bethesda, MD, Abstract E4, **71**, December 1997.

Chen ET. Fabrication and characterization of a novel amperometric biomimetic enzyme sensor 215th ACS National Meeting, Dallas, TX, March 29, 1998.

Chen ET. Error analysis for three commonly used clinical methods for blood glucose measurements at two accredited clinical laboratories. Annual Meeting of the American Association for Clinical Chemistry, Chicago, IL, August 2-6, 1998.

Chenault VM, Ediger MN, Durkin AJ, Waynant RW, Ansari RR. Spectroscopic detection of ocular pathologies in a nutritionally induced animal model of diabetes. FDA Science Forum on Regulatory Sciences, Washington, DC, December 5, 1997.

Choma TJ, Chwirut DJ, Polly DW. Biomechanics of long segment fixation: hook patterns and rod strain. 33rd Annual Meeting of the Scoliosis Research Society, New York, NY, September 20, 1998.

Chwirut DJ. Evolution of the engineering of intravascular stents. DCRND Brown Bag BRAINSTRETCHER, Rockville, MD, April 29, 1998.

Chwirut DJ. Anatomy of a performance standard. ASTM Committee F04 Workshop on the Development of Performance Standards for Medical Devices, Atlanta, GA, May 5, 1998.

Chwirut DJ, Oktay HS, Ryan T. Nitinol interventional cardiology devices - FDA's perspective. In SMST-97: Proceedings of the Second International Conference on Shape Memory and Superelastic Technologies, Pelton A, Hodgson D, Russell S, and Duerig T (eds.), published by SMST (Santa Clara, CA), 1997.

Connor AO, Anderson C, Chumakov KM, Ferreira JL, Flynn T, Hitchins V, Johannessen JN, Nduaka C, Ridge J, Sheehan D, Sistare F, Sobotka TJ, and Wekell MM. New methods development at the U.S. Food and Drug Administration. Proceedings of the 10th International Workshop on *In Vitro* Toxicology. Sparsholt, Winchester, United Kingdom, September 14-18, 1998.

Cress LW, Owen RD, Desta AB. Ornithine decaroxylase activity following exposure to 60-Hz magnetic fields. Annual Review of Research of Biological Effects of Electric and Magnetic Fields Form the Generation, Delivery, and Use of Electricity, San Diego, CA, November 9, 1997.

Cyr WH, Page BFJ. An explanation of the AAMI TIR for ethylene oxide residuals. The 8th Annual AAMI/FDA International Standards Conference on Medical Devices, Tysons Corner, VA, March 5-6, 1998.

Cyr WH, Lytle CD. Modification of ASTM 1671-95 test for protective clothing. ASTM meeting, Atlanta, GA, June 17-18, 1998.

Dubill PM. Performance standard for puncture resistance of sharps containers, *1997 FDA Science Forum on Regulatory Sciences*, Bethesda, MD, p. 57, December 1997.

Durkin AJ, Ediger MN. *In vitro* optical spectroscopic determination of silicone concentration in turbid media. FDA Science Forum on Regulatory Sciences, Washington, DC, December 5, 1997.

Durkin AJ, Ediger MN. Prediction of chromophore concentrations from fluorescence spectra of turbid samples using an artificial neural network. SPIE Photonics West, San Jose, CA, January 24-30, 1998.

Durkin AJ, Matchette LS, Ediger MN. Determination of silicone concentrations in blood from raman spectra using the method of partial least squares. SPIE BIOS '98, San Jose CA, February 1998.

Durkin AJ, Matchette LS, Ediger MN. Determination of silicone concentrations from raman spectra using the method of partial least squares (PLS). Optical Society of America (OSA) Topical Meeting on Biomedical Optical Spectroscopy and Diagnostics, Orlando, FL, March 8-12, 1998.

Ediger MN, Durkin AJ. Ultraviolet ellipsometric measurement of corneal absorption coefficient. Optical Society of America (OSA) Topical Meeting on Therapeutic Laser Applications, Orlando, FL, March 8-12, 1998.

Elespuru RK. Commentary. Invited talk at the Workshop on Alternative Animal Models in Radiofrequency Radiation, St. Pete's Beach, FL, June 7, 1998.

Elespuru RK. Making use of mode of action data in the assessment of carcinogenic risk to humans. Invited talk at the American Industrial Health Council (AIHC) Mutagenicity Subcommittee meeting, Washington, DC, August 4, 1998.

Fischman GS, Brown SA, Shwerin M. Validation study of the abrasion of titanium on titanium coatings for device stabilization. 1997 FDA Science Forum on Regulatory Sciences, Bethesda, MD, p.72, December 1997.

Furfine CS. FDAMA and medical device standards. AAMI Conference, Philadelphia, PA, June 2, 1998.

Gerhan JF, Hilbert SL, Salerno CT, Bianco RW. The development and evaluation of a swine model to assess the preclinical safety of intra-cardiac prosthetic devices. Workshop on Prosthetic Heart Valves: Future Directions, Hilton Head, SC, p. 7, February 22, 1998.

Goering PL. Toxicology and metabolism of mercury compounds. Program in Toxicology, University of Maryland, Baltimore, November 1997.

Godar DE, Lucas AD (poster presenter). Spectral dependence of UV-induced immediate and delayed apoptosis: the role of membrane damage. FDA Science Forum on Regulatory Science, Bethesda, MD, 1997.

Gonzalez G, Nueland CY, Zmudzka BZ. UVB-irradiated donor blood transfusions in renal transplantation: the CDRH perspective. FDA Photosciences Workshop, Gaithersburg MD, abstract 2:40, 1997.

Harris GR , Gammell PM. Effects of diffraction on the sensitivity of needle-type ultrasonic receivers. 16th International Congress on Acoustics and 135th Meeting of the Acoustical Society of America, Seattle, WA, June 20-26, 1998.

Harris GR. Pre-clinical shock wave testing. Gastroenterology and Urology Devices Advisory Panel Meeting, FDA, Rockville, MD, July 30, 1998.

Heaton HT. NVLAP calibration laboratories program. Sixth Annual Meeting of Council of Ionizing Radiation Measurements and Standards, National Institute of Standards and Technology, Gaithersburg, MD, November 12-14, 1997.

Heaton HT. Medical subcommittee: where we stand? Sixth Annual Meeting of Council of Ionizing Radiation Measurements and Standards. National Institute of Standards and Technology, Gaithersburg, MD, November 12-14, 1997.

Heaton HT. Medical subcommittee MPDs for next "needs" report. Sixth Annual Meeting of Council of Ionizing Radiation Measurements and Standards. National Institute of Standards and Technology, Gaithersburg, MD, November 12-14, 1997.

Heaton HT. IVB: dosimetry issues. Cardiovascular Radiation Therapy Meeting, Washington, DC, March 8-10, 1998.

Heaton HT. IDEs for intravascular brachytherapy: dosimetry issues. Workshop on Measurements and Standards for Intravascular Brachytherapy, Gaithersburg, MD, April 6-7, 1998.

Herman WA, Marlowe DE, Rudolph H. Future trends in medical devices technology: an expert survey. Rockville, MD, November 1997.

Herman WA, Marlowe DE, Rudolph H. Future trends in medical devices technology: an expert survey. NIH Biomedical Engineering Conference, NIH, February 1998.

Herman WA, Marlowe DE, Rudolph H. Future trends in medical devices technology: an expert survey. AIMBE Annual Meeting, National Academy of Sciences, March 1998.

Herman WA, Marlowe DE, Rudolph H. Future trends in medical devices technology: an expert survey. Rockville, MD, May 1998.

Herman WA, Marlowe DE, Rudolph H. Future trends in medical devices technology: an expert survey. Pac Med Tek, Honolulu, HA, July 1998.

Hilbert SL, Luna RE, Zhang J, Wang Y, Hopkins RA, Yu ZX, Ferrans VJ. Allograft heart valves: assessment of cell viability by confocal microscopy. 71st Scientific Session, American Heart Association, Orlando, FL, November 12, 1997. Circulation (Suppl) 96:I-508, 1997.

Hilbert SL, Luna RE, Zhang J, Wang Y, Hopkins RA, Yu ZX, Ferrans VJ. Evaluation of cell viability by confocal microscopy: potential tissue engineering applications. Workshop on Prosthetic Heart Valves: Future Directions, Hilton Head, SC, p 53, February 22, 1998.

Hilbert SL, Luna RE, Zhang J, Wang Y, Hopkins RA, Yu ZX, Ferrans VJ. Allograft heart valves: pathogenesis of the post-implantation loss of cuspal cellularity. Cryo 1998. 35th Annual Meeting of the Society for Cryobiology, July 15, 1998, p 69.

Hitchins VM, Merritt K. Decontaminating particles exposed to bacterial endotoxin (LPS). Transactions of the Society for Biomaterials, Volume XXI, p. 311, 1998.

Hitchins VM, Chapekar MS, Zaremba TG, Merritt K. Induction of nitric oxide, TNF-alpha, IL-4 and IL-6 by LPS in combination with silicone dioxide (SiO4) and amorphous silica in RAW 264.7

murine macrophages. Biological Response to Orthopedic Implants, Johns Hopkins University, Baltimore, MD, May 1-2, 1998.

Hutter JC, Luu HMD, Mehlaff PM, Killam AL, Dittrich HC. A fluorocarbon ultrasound contrast agent PBPK model. Proceedings of the 1998 Western Multi-Conference, Simulations in the Medical Sciences, San Diego, CA, Jan. 11-14, 1998.

Hutter JC, Luu, HMD. A PBPF model of a fluorocarbon ultrasound contrast agent. FDA Forum on Regulatory Sciences, Bethesda, MD, Abstract C4, 57, December, 1997.

Hutter JC, Sen S. Wallis RR, Lucas, AD. Cellulose acetate hemodialysis hollow fiber degradation and implications on human health. FDA Forum on Regulatory Sciences, Bethesda, MD, Abstract C5, 58, December 1997.

Ilev I, Waynant RW. Ultrabroadband tunable double-pass fiber Raman lasers for spectroscopic and sensor investigations in medicine and biology. Gordon Research Conference on Lasers in Medicine and Biology, Meriden, NH, June 14-19, 1998.

Kaplan DS , Picciolo GL., Moore MA, Kowolik MJ. Evaluation of respiratory burst of human leukocytes to pyrolytic carbon used in biomedical applications. Society for Leukocyte Biology 32nd National Meeting in Baltimore, MD, December 1997.

Kaplan DS, Picciolo GL, Delclos KB, Blaydes B. Regulatory tool for measuring host inflammatory and phagocytic responses to biomedical materials. FDA Forum on Regulatory Sciences, Bethesda, MD, Abstract B9. December 1997.

Krauthamer V. Intracellular calcium dynamics in cultured embryonic heart cells exposed to electric shocks. American Heart Association Scientific Conference on Ventricular Fibrillation: A Pediatric Problem, Seattle, WA, July 9-11, 1998.

Landry RJ, Levin RE, Bergman RS. CIE photobiological lamp safety standard. International Symposium on Measurements of Optical Radiation Hazards, NIST, Gaithersburg, MD, September 2, 1998.

Langone JJ. CDRH immunotoxicity testing guidance. ISO/TC 194 Meeting, Alexandria, VA, May 1998.

Luu HMD, Ekperigin E. Supercritical Fluid Extractions (SFE) of Various Polymers used in Medical Devices, FDA Forum on Regulatory Sciences, Abstract A17, 28, Bethesda, December 1997.

Lyle DB, Langone JJ. Inappropriate complement activation. Virtual Seminar on the FDA-Wide Immunotoxicity Electronic Network, October-November 1997.

Lyle DB. Beta cell replacement therapy in the treatment of diabetes. Virtual Seminar on the FDA-wide Immunotoxicity Electronic Network, February-March, 1998.

Lytle CD. An update on evaluation of materials as barriers to virus passage. CDRH Science Grand Rounds, September 14, 1998.

Malinauskas RA. The measurement of plasma hemoglobin in medical device hemolysis testing. American Society for Artificial Internal Organs, New York, NY, April 23-25, 1998.

Malinauskas RA. Plasma hemoglobin assays for *in vitro* hemolysis testing. 1997 FDA Forum on Regulatory Sciences, Bethesda, MD, December 1997.

Marlowe D. Implementation of the Food and Drug Modernization Act: 1998 Federal Technical Standards Workshop, Washington, DC, August 4, 1998.

Marlowe D. Overview of changes to FDA regulation of medical devices. International Conference on Advances in Biomaterials and Tissue Engineering, Capri, Italy, June 14, 1998.

Marlowe D. FDA recognition of standards. 8th Annual AAMI/FDA International Standards Conference on Medical Devices, McLean, VA, March 5-6, 1998.

Marlowe D. Conformity assessment in FDA recognition of standards. 8th Annual AAMI/FDA International Standards Conference on Medical Devices, McLean, VA, March 5-6, 1998.

Marlowe D. Results of an expert survey of developing technologies. Joint IEEE/ASME Meeting, Student Chapter, Catholic University of America, Washington, DC, April 9, 1998.

Matchette SL, Miller SA, Durkin AJ, Zmudzka B, Beer JZ, Virmani M, Pollard C. Interaction of UV radiation with mucosal tissue: comparison with skin. FDA Photosciences Workshop, Rockville, MD, November 1997.

McCormick DL, McDonald LJ, Gauger JR, Johnson TR, Cress LW, Owen RD, Desta AB, Savage RA, Lotz WG, Zhu H, Mandeville R. Ornithine decarboxylase activity in rat tissues exposed *in vivo* to complex power frequency magnetic field metrics: an interlaboratory program. Annual Review of Research of Biological Effects of Electric and Magnetic Fields Form the Generation, Delivery, and Use of Electricity, San Diego, CA, November 9, 1997.

McCormick DL, McDonald LJ, Loberg LI, Gauger JR, Mandeville R, Owen RD, Cress LW, Desta AB, Lotz WG, Savage RE, Zhu H. Ornithine decarboxylase activity in tissues from rats exposed to complex magnetic field metrics. Bioelectromagnetics Society 20th Annual Meeting, St. Pete Beach, FL, June 7, 1998.

McDonald LJ, Loberg LI, Mandeville R, Owen RD, Cress LW, Desta AB, Lotz WG, Savage RE, Zhu H, Gauger JR, McCormick DL. Ornithine decarboxylase activity in tissues from rats exposed to pure 60-Hz magnetic fields and magnetic field harmonics. Bioelectromagnetics Society 20th Annual Meeting, St. Pete Beach, FL, June 7, 1998.

McNamee S, Richardson DC, Kisielewski RW, Long MC. Dynamic testing of polymer membrane barrier integrity. FDA Forum on Regulatory Sciences, Bethesda, MD, Abstract C6, 58, December 1997.

Merritt K, Hitchins VM, Brown SA. Materials considerations in reusable devices. 1997 FDA Science Forum on Regulatory Sciences, Bethesda, MD, p.59, December 1997.

Merritt K., Hitchins VM, Brown SA. Materials consideration in reusable devices. AAMI/FDA Conference on Reprocessing Medical Devices: Designing, Testing and Labeling, Dallas, TX, November 5-7, 1997.

Merritt K, Hitchins VM, Brown SA, Woods TO. Cleaning biological debris from materials and effects of the cleaning process on material properties. *Transactions of the Society for Biomaterials*, vol.XXI, p. 372, 1998.

Miller SA, James RH. Sunlamp standards: how FDA's differ from European standards. FDA Photosciences Workshop, Rockville, MD, November 1997.

Miller SA, Grossman LW, Byrnes GA, Mazur DO. Laser characteristics through fundus contact treatment lenses: risk for laser induced cataracts. FDA Science Forum, Bethesda, MD, December 5, 1997.

Miller SA, Sayre RM, Cyr WH. Comparison of UV emissions from sunlamps and from solar exposure through sunscreens: the potential importance for melanoma. American Society for Photobiology, Snowbird, UT, July 11-15, 1998.

Miller SA, James RH. CDRH activities in lamp evaluation. International Symposium on Measurements of Optical Radiation Hazards, National Institute of Standards and Technology, Gaithersburg, MD, September 1-3, 1998.

Moore MA, Kaplan DS, Wallis RR., Picciolo GL, Kowolik MJ. Neutrophil interaction with cellulose acetate materials *in vitro*. Poster Presentation at the 6th Annual Research Day for the Indiana University School of Dentistry, Indianapolis, IN, April 1998.

Moore MA, Kaplan, DS, Wallis RR, Picciolo GL, Kowolik MJ. The effect of cellulose acetate materials on the oxidative burst of human neutrophils. Poster Presentation/Oral discussion at the 17th European Workshop on the Cell Biology of Phagocytes in Catania, Italy. *European Journal of Haematology* **60**:5, May 1998.

Morehouse CA, Owen RD. Exposure to a 50 μT, 60-Hz magnetic field does not induce MYC in Daudi Cells. Annual Review of Research of Biological Effects of Electric and Magnetic Fields Form the Generation, Delivery, and Use of Electricity, San Diego, CA, November 9, 1997.

Myers KJ. Methods for the evaluation and validation of image quality. Image Perception in Radiology (NIH workshop), Chevy Chase, MD, October 21, 1997.

Neale AR, Merritt K, Brown SA. Evaluation of a dye penetration test for package integrity. 1997 FDA Science Forum on Regulatory Sciences, Bethesda, MD, p 45, December 1997.

Nino HV. Keynote speaker. El Impacto Administrativo en la Calidad de la Practica Medica. (The Administrative Impact on the Quality of Medical Practice) in Spanish. First Forum on Quality of Health. Guanajuato, Gto. Mexico, June 1998.

Nueland CY, Gonzalez G, Zmudzka BZ. UVR^{R} Photopheresis system: background and CDRH issues. FDA Photosciences Workshop, Gaithersburg MD, abstract 2:00, 1997.

Owen RD (platform speaker). Coordinated efforts of the US Health and Safety Agencies International Conference on Mobile Phones and the Community. Sponsored by the Ireland Department of Health, Department of Environment, and Department of Public Enterprise, Dublin, Ireland, March 6, 1998.

Owen RD (platform speaker). FDA ELF-EMF research and regional exposure facility. Joint Meeting of the National EMF Advisory Committee and the Federal EMF Interagency Committee, Washington, DC, May 8, 1998.

Rudolph H. Risk management: a regulatory perspective. Association for the Advancement of Medical Instrumentation International Standards Conference, Crystal City, VA, March 5, 1998.

Rudolph H. Future standardization requirements: a regulator's viewpoint. International Electrotechnical Commission Advisory Committee on Standards Meeting, Toronto, Ontario, Canada, May 6, 1998.

Rudolph H. New developments in device regulation. Western Association of Food and Drug Officials, Jackson, WY, September 14, 1998.

Sayre RM, Miller SA. UV sources used for human exposure. Research Workshop on Risks and Benefits of Exposure to UV Radiation and Tanning, Bethesda, MD, September 16-18, 1998.

Schroeder LW (invited speaker) Biostable polymers: measuring and predicting stability. ACS Division of Polymeric Materials: Science and Engineering, 216th ACS National Meeting, Boston, Abstract 224, August 23-38, 1998.

Shope TB. Deterministic effects of interventional radiology procedures. WHO Radiation Emergency Preparedness and Assistance Network Meeting, Rio de Janeiro, Brazil, November 10, 1997.

Shope TB. US Food and Drug Administration regulations for fluoroscopic x-ray systems and concepts for changes. Workshop on the Implementation of the New International Standards on Radiation Protection and Safety, Institute of Radiation Protection and Dosimetry, Rio de Janeiro, Brazil, November 7, 1997.

Shope TB. FDA activities related to fluoroscopically guided interventional procedures. The 30th Annual National Conference on Radiation Control, Mesa, AZ, May 14-21, 1998.

Shope TB. FDA efforts to ensure Year 2000 compliance of medical devices and manufacturers. RX2000 Solutions Institute Special Interest Group Meeting, Arlington, VA, September 25, 1998.

Stratmeyer ME. Biomaterials and biocompatibility testing. 8th Annual AAMI/FDA International Standards conference on Medical Devices, McLean, VA, March 5-6, 1998.

Stratmeyer, ME. Case study: natural rubber (latex) allergies. Biological Safety Assessment of Medical Devices, Munich, Germany, December 3-4, 1997.

Stratmeyer, ME. Latex issues. FDLI Medical Device Update '98, Washington, DC, June 24-25, 1998.

Stratmeyer, ME. New approach to biocompatibility testing for materials. Toxicology Forum, Washington, DC, February 2-5, 1998.

Tomazic VJ, Merritt K, and Umbreit TH. Significance of the size and chemical composition of biomaterial particles on the deposition pattern and the host response in mice. American Association of Immunologists, San Francisco, CA, 1997.

Wagner RF. Assessment of diagnostic modalities. Center for Biologics and Evaluation Research/FDA, Washington, DC, April 20, 1998.

Wagner RF, Gagne RM, Myers KJ, Wear KA. Image quality issues for computer-aided diagnosis. 1st International Workshop on Computer-Aided Diagnosis, Chicago, IL, September 21, 1998.

Wagner RF, Mossoba JT, Chan HP, Sahiner B, Petrick N. Finite-sample dependence of classifier assessment in computer-aided diagnosis. 1st International Workshop on Computer-Aided Diagnosis, Chicago, IL, September 22, 1998.

Wagner RF, Gagne RM, Myers KJ, Wear KA. Model observers for imaging system assessment. AAPM Symposium on the Assessment of Diagnostic Imaging Systems, Annual Meeting of the AAPM, San Antonio, TX, August 1998.

Walsh DL. Environmental degradation of natural rubber latex gloves: an update. ASTM D11.40 Modified Lowry Protein Working Group Meeting, Baltimore, MD, May 21, 1998.

Walsh DL. Accelerated aging of natural rubber latex gloves. ASTM D11.40 Consumer Rubber Products 52nd Meeting, Atlanta, GA, June 16, 1998.

Waynant RW. Lasers in medicine and biology. National Capital Section of Optical Society of America, Washington, DC, January 20, 1998.

Waynant RW. Lasers in medicine and biology, IEEE Virginia Mountain Section, Blacksburg, VA, April 16, 1998.

Waynant RW, Chakrabarti K, Kaczmarek R, Suleiman O, Rowberg A. Improved sensitivity and specificity of mammograms by producing uniform luminance from viewboxes. Society for Computers in Radiology Applications, Baltimore, MD, June 5, 1998.

Waynant RW, Gannot I, Ilev I. Mid IR waveguides and fibers for FEL laser surgery. 20th Annual Conference on Free Electron Lasers, Williamsburg, VA, August 19, 1998.

Wear KA, Garra BS. Assessment of bone density using broadband ultrasonic backscatter. Proceedings of the 22nd International Symposium Ultrasonic Imaging Tissue Characterization, June 1997.

Witters D. Electromagnetic Interference with Medical Devices: Continuing Challenges, 33rd Annual AAMI Conference, Philadelphia, PA, May 31, 1998.

Witters D. Electromagnetic interference with medical devices: Implications in medical information technology. IEEE Engineering in Medicine and Biology Special Topic Conference on Information Technology Applications in Biomedicine Washington, DC, (ITAB-98), May 16, 1998.

Witters D. Electromagnetic interference with medical devices: concerns and tools for addressing the challenges. Metropolitan Washington Federal Safety Health Council 16th Annual Safety and Health Conference, Arlington, VA, June 10, 1998.

Witters D. The management of electromagnetic energy around medical devices. Healthcare Informatics Telecom Network video conference, Bethesda, MD, May 13, 1998.

Witters D. Medical device electromagnetic interference: medical telemetry interactions with DTV and implications for telemedicine. Joint Federal Working Group on Telemedicine, Washington, DC, May 7, 1998.

Witters D. FDA recognition and use of medical device EMC Standards. AAMI/FDA International Standards Conference on Medical Devices, Tysons Corner, VA, March 5, 1998.

Witters D, Silberberg J. FDA EMC activities. University of Oklahoma Wireless EMC Forum 4: Focus on medical/automobile electronics-wireless device compatibility, Dallas, TX , October 27-28, 1997.

Woods TO. The effect of sodium azide on the strength of synthetic absorbable sutures *in vitro.* Transactions of the 24th Annual Meeting of the Society for Biomaterials, San Diego, CA, p. 272, April 22 – 26, 1998.

Zmudzka BZ (speaker), Beer JZ. Analysis of risks from HIV activation and immune modulation in UVB and PUVA therapies. *Photochem. Photobiol.* **67(S)**, 17S, 1998.

Zmudzka BZ (poster presenter), Adams ML, Beer JZ, Bethke FR, Cruz PD, Lightfoote MM, Shearer GM. Lymphokine Profiles in Psoriasis Patients Treated with UVB Therapy. FDA Forum on Regulatory Sciences, Washington, DC, abstract I-24, 116, 1997.

Zmudzka BZ (speaker), Beer JZ, Nueland CY, Gonzalez G. UV-induced suppression of the immune system: regulatory and laboratory aspects. FDA Photosciences Workshop, Gaithersburg MD, abstract 1:55, 1997.

Appendix C - Academic Affiliations of OST Staff

October 1, 1997 - September 30, 1998

Bassen, Howard, M.S.	George Washington University Department of Electrical Engineering and Computer Science Adjunct Professor
Fischman, Gary S., Ph.D.	Johns Hopkins University Department of Engineering Instructor
	Catholic University of America Bioengineering Graduate Program Advisory Board
	Alfred University Biomaterials Program Advisory Board
Goering, Peter L., Ph.D.	University of Maryland School of Medicine Graduate Program in Toxicology Adjunct Professor
Grossman, Laurence W., Ph.D.	Georgetown University Medical Center Department of Radiology Adjunct Associate Professor
Krauthamer, Victor, Ph.D. for Health Services	Uniformed Services University
	Department of Physiology Adjunct Assistant 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
Picciolo, Grace L.	Clemson University Department of Bioengineering Adjunct Professor
Waynant, Ronald W., Ph.D.	Catholic University of America Electrical Engineering Department Adjunct Associate Professor
Waynant, Ronald W., Ph.D.	Uniformed Services University of the Health Sciences Radiology Department

Appendix D - OST Patents

October 1, 1997 – September 30, 1998

PATENTS ISSUED:

Bassen H, Krauthamer V. US Patent #5,678,550: Apparatus and method of in situ detection of areas of cardiac electrical activity. October 21, 1997.

Marchlinski F, Schwartzman D, Chang I. US Patent #5,673,704: Method of using endocardial impedance for determining electrode-tissue contact. October 7, 1997.

Schmukler R, Lytle CD. US Patent #5,671,754: Viral-proofing a protective barrier, 1997.

Appendix E – OST Research Seminars

October 1, 1997 – September 30, 1998

Barrett HH, University of Arizona. Likelihood-generating functions. CDRH, Rockville, MD, October 27, 1997.

Barrett HH, University of Arizona. Quantum optics and image science: two sides of the same coin? CDRH, Rockville, MD, March 3, 1998.

Beiden S, University of West Virginia. Contemporary problems in computational physics. CDRH, Rockville, MD, September 8, 1998.

Goering PL. The metabolism and toxicology of mercury. Program in Toxicology, University of Maryland School of Medicine, Baltimore, MD, November 19, 1997.

Myers MR. A computer model for simulating virus transport through synthetic barriers. State University of New York at Binghamton Mechanical Engineering Seminar Series Colloquium, February 6, 1998.

Owen RD. Coordinated efforts of the US Health and Safety Agencies. International Conference on Mobile Phones and the Community. Sponsored by the Ireland Department of Health, Department of Environment and Department of Public Enterprise, Dublin, Ireland, March 6, 1998.

Owen RD. FDA Elf-EMF research and regional exposure facility. Joint Meeting of the National EMF Advisory committee and the Federal EMF Interagency Committee, Washington, DC, May 8, 1998.

Rolland JP, University of Central Florida. Synthesis of biomedical tissue. CDRH, Rockville, MD, March 2, 1998.

Witters D. A brief overview of FDA's approach to medical device electromagnetic interference. NIH Hospital Administration Seminar, Bethesda, MD, March 10, 1998

Appendix F - Research Contracts and Interagency Agreements

October 1, 1997 – September 30, 1998

Armed Forces Institute of Pathology (FDA-224-82-5000). To collaborate in a pilot project intended to assess the feasibility/usefulness of a heart valve study group.

Biocon, Incorporated (FDA-223-96-6050). Housing and care for experimental animals.

Environmental Protection Agency (FDA-224-97-6010). Development of animal models for reproductive and development toxicity risk assessments.

Mentor Technologies (FDA-223-94-6015). The effects of ionizing and non-ionizing radiation..

National Academy of Sciences (FDA-223-93-6007). To establish a CDRH/FDA research associateship program through the NRC of the NAS to further the purposes of FDA in research.

National Institutes of Standards and Technology (FDA-224-93-6015). Secondary calibration – National Voluntary Laboratory Accreditation Program.

National Institutes of Environmental Health Sciences (FDA-224-94-6013). Effects of extremely low frequency (ELF) fields on selected human cell lines.

National Research Council (FDA-223-93-6007). To establish a CDRH/FDA research associateship program through the National Research Council to further the purposes of FDA in research.

Office of Emergency Preparedness (FDA-224-94-6011). Support services for modifying emergency response equipment.

Office of Naval Research (FDA-224-92-6007). Evaluation of single crystal sapphire fibers for medical applications.

Office of Naval Research (FDA-224-98-6007). Waveguide and fiber optic delivery for medical application of free electron lasers.

Sachs-Freeman, Inc. (FDA-223-96-6051). Characterize reference equipment used to determine the dosimetry of mammography x-ray beams.

U.S. Department of Energy (FDA-224-88-6064). Establish and conduct a research fellowship program.

Air Force Office for Scientific Research (FDA-224-98-6005). Support to CDRH for infrared fiber and waveguide testing.

National Aeronautics and Space Administration (FDA-224-98-6013). Collaborative research program: use and testing of a novel fiber optic eye diagnostic instrument in an animal model of diabetes.

Uniformed Services University of the Health Sciences (FDA-224-98-6015). Maintenance of animals for the pathophysiology of diabetes for end organ studies.

Naval Research Laboratory (FDA-224-98-6018). Testing of chalcogenide fibers for medical applications.

Naval Research Laboratory (FDA-224-98-6019). Optical coherence tomography for medical applications.

Appendix G – Standards Organizations

October 1, 1997 – September 30, 1998

A. NATIONAL STANDARDS ORGANIZATIONS

American Institute of Ultrasound in Medicine (AIUM)
Board of Directors
Joint Standards Task Group - Safety Standard
Technical Standards Committee
- Digital Measurement Subcommittee
- Doppler Standards Subcommittee
- National Electrical Manufacturers Association
- Nomenclature Subcommittee
- Scanner Equivalence Subcommittee

American National Standards Institute (ANSI)
Z 3 11 Photobiological Safety of Lamps and Lighting Systems Subcommittee
Accreditation Committee
Acoustical Standards Management Board (ASA)
C 16 ESD Performance
Executive Standards Council
Government Members Council
Healthcare Informatics Standards Planning Board
International Conformity Assessment Committee (ICAC)
Medical Devices Standards Board (MDSB)
N 43 Equipment for Non-Medical Radiation Applications
U.S. National Committee to EEC
Z 080 Ophthalmic Standards
- Subcommittee on Eye Implants
- Z80.7 IOL's
  - Operating Microscopes

Z 136 Biological Effects of Lasers
Z 136 Safe Use of Lasers Committee
- Z 136.4 Laser Control Measurements Subcommittee

Z 3 11 Photobiological Safety of Lamps and Lighting Systems Subcommittee (IES)

American Society for Testing and Materials (ASTM)
Board of Directors
C 28 Advanced Ceramics
Committee on Technical Committee Operations (COTC)
D 11 Rubber
- D 11.40 Consumer Rubber Products Glove Task Group
- D 11.40 Consumer Rubber Products Latex Chemical Sensitivity Task Group
- D 11.40 Consumer Rubber Products Latex Protein Task Group

E 28 Mechanical Testing
- E 28.03 Uniaxial Testing

E 36 Conformity Assessment

E 48 Biotechnology
- E 48.02 Characterization and Identification of Biological Systems Subcommittee
  - E 48.02.03 Task Group on Viruses

F 04 Medical & Surgical Materials & Devices
- F 04.01 Division I Resources
  - F 04. 11 Polymeric Materials
  - F 04.11.04 Poly-L-Lactic Acid (PLLA)
  - F 04.11.05 Bioresorbable Polymer Terminology
  - F 04.11.06 Bioabsorbable Polymer-Degradation TM's
  - F 04.11.07 Acrylic Bone Cement
  - F 04.11.08 Revision of F648 UHMWPE
  - F 04.12 Metallurgical Materials
  - F 04.13 Ceramic Materials
  - F 04.13.04 Rev F603-Polycrystalline Alumina
  - F 04.13.05 Calcium Phosphate Coatings (CPC) Crystalline Characterization
  - F 04.13.09 Calcium Phosphate Coatings (CPC) Environmental Stability
  - F 04.13. 10 Zirconia/Zirconium Oxide
- F 04.14 Composite Materials
  - F 04.14.01 Composite I-lip Stem Testing
- F 04.15 Material Test Methods
  - F 04.15.03 Tension Testing Porous Materials
  - F 04.15.07 PLA Degradation
  - F 04.15.08 Coatings Abrasion
  - F 04.15.11 MR Compatibility of Implant Materials and Medical Devices
- F 04.16 Biocompatibility Test Methods
  - F 04.16.01 Biocompatibility Testing Relating to Particulate Implant Debris
  - F 04.16.05 Recovery of Foreign Particulates from Tissue
- F 04.18 Device Retrieval Analysis
- F 04.19 Corrosion of Implant Materials

F 04.02 Division II Orthopaedic Devices
- F 04.21 Osteosynthesis
  - F 04.21.01 Bone Screws
  - F 04.21.02 Bone Screw Testing Methods
  - F 04.21.03 Intramedullary Rods
  - F 04.21.04 External Fixation Devices
  - F 04.21.05 Bone Staples
  - F 04.21.06 Fixation Wires
  - F 04.2 1. 11 Bone Plates
- F 04.22 Arthroplasty
  - F 04.22.01 Total Hip w/ Femoral Stems
  - F 04.22.09 Femoral Stem Test Methods
  - F 04.22. 10 Hip Wear
- F 04.25 Spinal Devices

F 04.03 Division III Medical/Surgical Devices
- F 04.30 Cardiovascular Standards (formerly F 04.40)
- F 04.31 Neurosurgical Standards (formerly F 04.50)
- F 04.33 Medical/Surgical Instruments (formerly F 04.65)
  - F 04.33.01 Needle Disposal/Puncture Resistance
- F 04.36 Cotton Products for Medical Use (formerly F 04.80)

F 04.04 Division IV Tissue Engineered Medical Products
F 04. 10 Division IX Administrative
- F 04.90 Executive Subcommittee
- F 04.93.03 Neurosurgical Iransplants
- F 04.95 ISO/TC 168
- F 04.96 ISO/TC 194

F 23 Protective Clothing
- F 23.40 Biological

F 29 Anesthetic and Respiratory Equipment
- F 29.03 Division Three on Ventilators & Ancillary Devices
- F 29.03. 10 Pulse Oximeters

F 30 Emergency Medical Services
G 03 Durability of Non Metallic Materials

Association for the Advancement of Medical Instrumentation (AAMI)
Apnea. Monitoring Committee
Biological Evaluation Committee
- Animal Protection Aspects WG (serves as US sub-TAG for ISO TC 194, WG 3)
- Cytotoxicity WG (serves as US sub-TAG for ISO TC 194, WG 5)
- Degradation Aspects Related to Biological Testing WG (serves as US sub-TAG for ISO TC 194, WG 2)
- Genatox, Carcinogenicity, Reproductive Toxicity WG (serves as US sub-TAG for ISO TC 194, WG 6)
- Irritation & Sensitization WG (serves as US sub-TAG for ISO TC 194, WG 8)
- Sample Preparation & Reference Materials WG (serves as US sub-TAG for ISO TC 194, WG 12)
- Systemic Toxicity WG (serves as US sub-TAG for ISO TC 194, WG 7)

Cardiac Valve Prostheses Committee
ECG Committee
- Arrhythmia Monitoring WG (serves as US sub-TAG for IEC 62D, WG 2)
- Diagnostic ECG and Cardiac Monitor WG (serves as US sub-TAG for IEC 62D, WG 4/5)
- Electrode WG (serves as US sub-TAG for IEC 62D, WG 6)
- Signal Averaging WG (serves as US sub-TAG for IEC 62D, WG 7)

EMC Committee
Electrical Safety Committee
International Standards Committee
Mechanical Circulatory Support Systems Committee
- SP10 Electronic or Automated Sphygmomanometers

Medical Device Software Committee
Neurosurgery Committee

Implantable Neurostimulator WG (serves as US sub-TAG for IEC 62D, WG 2)
Pacemaker Committee (serves as US sub-TAG for ISO TC 150, SC 2, WG 2 & IEC 62D, WG 6)
Standards Board
Sterilization Standards Committee
Microbiological Methods WG (serves as US sub-TAG for ISO TC 198, WG 8)
Returned Devices Decontamination WG (serves as US sub-TAG for ISO TC 198, WG 80)
Reusable Devices Resterilization WG (serves as US sub-TAG for ISO TC 198, WG 8 1)
Reusable Supplies Decontamination WG (serves as US sub-TAG for ISO TC 198, WG 82)
Sterilization Residuals WG (serves as US sub-TAG for ISO TC 198, WG 63)
Glutaraldehyde & Formaldehyde TG I (WG 63)
Waveform Testing Committee

Institute of Electrical and Electronics Engineers (IEEE)
C 63 Electromagnetic Compatibility
C63.1 Electromagnetic Compatibility
C63.8 Medical Device Electromagnetic Compatibility Measurements
C 63.19 Task Group on Method of Measurements for Compatibility Between Wireless Communication Devices and Hearing Aids
SC 8 on Medical Device EMC Test Methods
WG on Ad Hoc EMC Measurement Techniques
P 1140 Measurement of Electrical & Magnetic Near Fields in Frequency Range of 5Hz & 3 0MHz
P 1140.1 Measurement Techniques for ELF & VLF Magnetic Fields & Electric Fields from Desktop Computer Displays & Associated Desktop Devices
SCC 28 Sectional Committee on Radiofrequency Radiation Hazards
SC I Subcommittee on Instrumentation
SC 2/3 Terminology Standards and Units of Measurement
SC 4 Safety Levels and/or Tolerances with Respect to Personnel
WG 03 High Frequency Effects (From Low Frequencies to and Including the Resonance Region)
SCC 28 Sectional Committee on Radiofrequency Radiation Hazards Executive Committee
SCC 34 Standards Coordinating Committee on Certification of Radiofrequency Safety Wireless Handsets
Software Safety Planning Group
Technical Committee on Ultrasonics, Ferroelectrics, and Frequency Control (UFFC)

Association for the Advancement of Rehabilitation Technology/Rehabilitation Society of North America (RESNA)

National Committee for Clinical Laboratory Standards (NCCLS)
Area Committee on Automation

Area Committee on Hematology Subcommittee on Point-of-Care Hemostasis/Coagulation
Area Committee on Immunology and Ligand Assay Subcommittee on Digoxin
Area Committee on Microbiology Subcommittee on Culture Media
Area Committee on Molecular Methods
    Subcommittee on Immunohistochemical Procedures
    Subcommittee on Molecular Genetics
    Subcommittee on Molecular Microbiology
Delegate
Standing Committee: International Relations (ISO TC 212)
Standing Committee: Nominating
Standing Committee: Standards Management

National Council on Radiation Protection and Measurements (NCRPM)
SC 66 Effects of Ultrasound

National Electrical Manufacturers Association (NEMA)
Digital Imaging and Communications Standards Committee WG 11 Display Function

Association for the Advancement of Rehabilitation Technology (RESNA)
Wheelchairs SC on Powered Wheelchair EMC

Underwriters Laboratory (UL)
Medical Industry Standards Group

United States Pharmacopeia (USP)
Official CDRH Correspondent

B. INTERNATIONAL STANDARDS ORGANIZATIONS

Deutsches Institut fur Normung (DIN) - German Institute for Standardization

AAE 9 Immunology, Serodiagnostics of Infectious and Immunological Diseases

ESD Association's Standards Committee

International Commission on Illumination (CIE)

Div. 6 - Photobiology and Photochemistry

    ESD Association's Standards Committee

International Electrotechnical Commission (IEC)
TC 29 Electroacoustics WG 13 Hearing Aids
TC 61 Safety of Household and Similar Electrical Appliances

WG 16 Ultraviolet Radiation

SC 61B Safety of Microwave Ovens TC 62 Electrical Equipment in Medical Practice

WG 02 Safety of Computer Systems Used in Medical Electrical Equipment

SC 62A Common Aspects of Electrical Equipment Used in Medical Practice TAG
Secretary's Advisory Group
WG 01 Safety
WG 13 Electromagnetic Compatibility
WG 15 Risk Management
WG 16 Electric Shock
WG 17 Mechanical Hazards
WG 18 Overheating, Fire Protection and Additional Hazards (combined WG 18 & 19)

SC 62B Diagnostic Imaging Equipment TAG \
WG 15 High Voltage Generators
WG 19 Mammographic Anti-Scatter Grids & Mammographic Cassettes
WG 22 Ultrasound Diagnostic Equipment
WG 24 Safety of X-ray Equipment for Interventional Procedures
WG 25 Safety of X-ray Equipment for Computed Tomography

SC 62C Equipment Radiotherapy, Nuclear Medicine and Radiation Dosimetry TAG
WG 03 Performance /of Dosemeters

SC 62D Electromedical Equipment TAG
WG 01 Multiparameter Patient Monitoring Equipment
WG 06 Cardiac Pacemakers
WG 11 Extra-corporal Shock Wave Lithotripsy Equipment sub-TAG
WG I Monitoring Equipment SC 62D Electromedical Equipment TAG
Electrocardiographs (ECG)
Ultrasonic Medical Diagnostic Equipment
WG 2 Therapy and Surgery Equipment SC 62D Electromedical Equipment TAG
Ultrasound Therapy sub-TAG
TC 65 Systems Aspects
WG 10 Functional Safety of Programmable Electronic Systems
TC 77 Electromagnetic Compatibility
TC 87 Ultrasonics
WG 08 Ultrasonic Field Measurement
WG 12 Ultrasound Exposure Parameters
U.S. Coordinating Committee on Electromagnetic Compatibility

ISBT Automation and Data Processing Working Group

International Organization for Standardization (ISO)
TC 056 Dependability WG 03 Equipment Reliability Verification

TC 150 Implants for Surgery
- SC I Materials
- SC 2 Cardiovascular Implants TAG
  - WG 01 Cardiac Valves
  - WG 02 Cardiac Pacemakers
  - WG 04 Blood Oxygenators
  - WG 05 Retrieval and Analysis of Implants
  - WG 09 Implant Data Sets
- SC 3 Neurological Implants
- SC 4 Bone and Joint Replacements
  - WG 02 Knee Wear
- SC 5 Implants for Osteosynthesis

TC 172 Optics and Optical Instruments
- SC 7 Ophthalmic, Optics and Instruments
  - WG 06 Ophthalmic Optical Instruments
  - WG 07 Medical Ophthalmic Products
- SC 9 Electro-optical Systems (and Lasers)
  - WG 0 1 Terminology and Test Methods
  - WG 02 Interfaces and System Specifications for Lasers
  - WG 03 Safety
  - WG 04 Laser Systems for Medical Applications
  - WG 05 Laser Systems for General Applications
  - WG 06 Optical Components and Their Test Methods
  - WG 07 Electro-optical Systems Other Than Lasers

TC 173 Technical Systems and Aids for Disabled or Handicapped Persons
- SC I Wheelchairs WG 10 Requirements and Test Methods for Electromagnetic Compatibility of Powered Wheelchairs and Motorized Scooters

TC 194 Biological Evaluation of Medical Devices
- WG 02 Degradation Aspects Related to Biological Testing Ceramics Task Force
- WG 02 Degradation Aspects Related to Biological Testing Polymers Task Force

TC 194 Biological Evaluation of Medical Devices
- WG 02 Degradation Aspects Related to Biological Testing sub-TAG
- WG 03 Animal Protection Aspects sub-TAG
- WG 05 Cytotoxicity sub-TAG
- WG 06 Mutagenicity, Cancerogenicity, Reproductive Toxicity sub-TAG
- WG 07 Systemic Toxicity sub-TAG
- WG 08 Irritation, Sensitization
- WG 11 Ethylene Oxide & Other Sterilization Process Residues (Joint TC 194-TC 198)
- WG 12 Sample Preparation and Reference Materials
- WG 13 Toxicokinetic Study
- WG 14 Material Characterization
- WG 15 Strategic Approach to Biological Assessment

TC 198 Sterilization of Health Care Products
- WG 04 Biological Indicators sub-TAG
- WG 08 Microbiological Methods sub-TAG

WG 12 Instructions for Processing of Resterilizable Medical Devices
TC 210 Quality Management and Corresponding General Aspects for Medical Devices
WG 02 General Aspects Stemming from the Application of Quality Principles to Medical Devices
WG 04 Application of Risk Management to Medical Devices
ISO/IECJTCI/SC7 TAG, Software Engineering

International Commission on Non-Ionizing Radiation Protection (ICNIRP) Standing Committee
3 – Physics and Measurements

Appendix H - 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