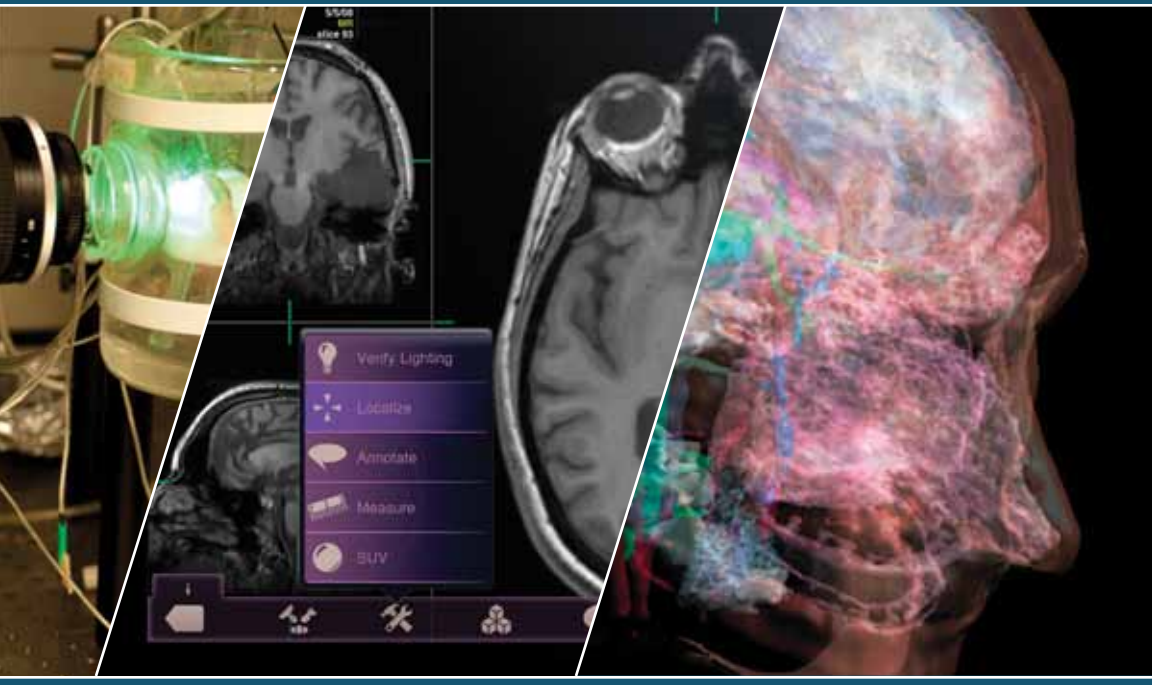
Regulatory Science in FDA's Center for Devices and Radiological Health:

A VITAL FRAMEWORK FOR PROTECTING AND PROMOTING PUBLIC HEALTH



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A VITAL FRAMEWORK FOR PROTECTING AND PROMOTING PUBLIC HEALTH

Published by
Food and Drug Administration,
US Department of Health and Human Services

This publication is available on FDA's website at
http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHReports/default.htm

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http://www.fda.gov/MedicalDevices
http://www.fda.gov/Radiation-EmittingProducts/

Foreword

In the U.S. today, patients and their doctors have ready access to safe, effective medical devices that can save lives and improve health. This is due in large measure to advances in regulatory science, which provides the tools, standards, and approaches needed to evaluate the safety, effectiveness, quality and performance of the products we regulate.

In FDA's Center for Devices and Radiological Health, our efforts in regulatory science help foster a robust medical device industry by reducing the time and resources needed to develop and assess new products. This promotes innovation, supports the manufacture of high quality products, and speeds the rate at which technologies reach the market.

This report provides a broad overview of the many scientific activities in which we are currently engaged, as well as what we see as important regulatory science targets in the future as science and technology continue to evolve.

We hope you find it useful and informative.

JEFFREY SHUREN, M.D., J.D.
Director, Center for Devices and Radiological Health
Food and Drug Administration

How This Report is Organized

The body of the report is an overview briefly describing the role of regulatory science in device development, pre-market and post-market assessment, and manufacturing. We also explain the seven major priority areas that comprise the focus of regulatory science in CDRH, with examples of each. They are:

A. Advancing Medical Device Innovation and Evaluating New and Emerging Technologies

B. Improving Device Quality and Manufacturing

C. Analyzing Medical Device Performance

D. Improving Medical Device Safety

E. Developing Novel Ways to Use Clinical Data in Evaluating Medical Devices

F. Protecting Against Emerging Infectious Diseases and Terrorism

G. Improving Health of Pediatric and Other Special Populations.

In Appendix I, "Summary of Current Regulatory Science Activities in CDRH," we expand on the key priorities by describing some of the regulatory science projects we are currently engaged in.

In Appendix II, "Looking to the Future: New Directions for Regulatory Science in CDRH," we discuss some of the new trends in science and medicine that will shape regulatory science efforts in the future.

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Overview of Regulatory Science in the Center for Devices and Radiological Health

INTRODUCTION

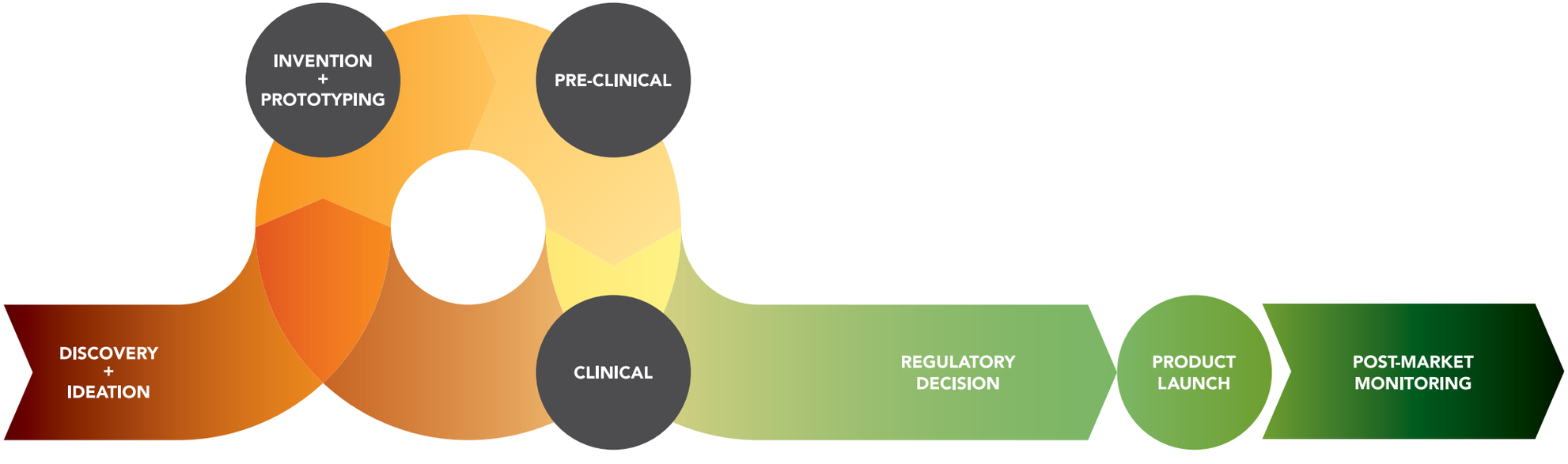
Within the U.S. Food and Drug Administration (FDA), the Center for Devices and Radiological Health (CDRH) is responsible for assuring the safety and effectiveness of a broad array of medical devices, ranging from implantable defibrillators to CT scanning devices and from artificial hips to software programs used in diagnosing disease. We are committed to fostering innovation in device development, assessment, and manufacturing, and to providing the public with accurate, science-based information about the products we oversee.

As technology advances, medical devices are becoming increasingly complex. We must be able to anticipate these advances, creating the scientific tools that will assist the industry in developing new products and assessing their safety, effectiveness, quality, and performance. Regulatory science enables us to do this.

Regulatory science activities include researching how new devices interact with the body, developing test methods for new technologies, testing products to identify root causes of failure, and developing epidemiological methods to help conduct postmarket studies of devices.

REGULATORY SCIENCE AND DEVICE DEVELOPMENT

Advances in regulatory science can streamline many aspects of the device development process. This facilitates innovation by sharply decreasing the cost and time involved in designing medical devices. The medical device development process can be depicted as follows:



As noted in the diagram, the pathway to successful device development is not a straight line. It is cyclical and iterative as ideas are generated, tested, improved, re-tested, optimized and finalized.

Regulatory science can foster innovation and patient safety in all aspects of the product life cycle. It can help medical device developers to detect design flaws earlier and at lower cost, and thus develop the final model of a successful technology more quickly and efficiently. Regulatory science also permits device developers to better test the durability of a device or how it performs under duress, reducing the likelihood of complications when the device is used in actual patients. This

information is critical in the development and manufacturing of safe and effective medical devices.

Advances in regulatory science can lead to new, innovative devices. For example, for many years, patients with implanted pacemakers were denied the benefits of MRI scanning because the electromagnetic effects of the MRI could cause the pacemaker to overheat or move out of position. Our electromagnetic compatibility lab, collaborating with industry and academia, was able to analyze the effects of MRI systems on pacemakers and to develop techniques for predicting the safety of specific pacemaker designs in MRI scanners. This enabled us to approve the first implantable pacemaker intended to be compatible with MRI exams. As a result of this work, there are MRI-compatible pacemakers and other implantable devices on the market today and other devices are presently in development.

REGULATORY SCIENCE AND DEVICE ASSESSMENT

As a medical device is developed and evaluated, regulatory science plays an important role in evaluating its benefit-risk profile. It provides a vehicle through which we collaborate with other stakeholders in developing tools that help manufacturers develop innovative products, and it helps manufacturers and us assess those products. The result is a more effective, efficient, and timely approach to device development, assessment, and manufacturing.

In the premarket design stage, new regulatory science advances mirror the emergence of new types of products, such as those used in modern minimally-invasive diagnosis and therapy. For example, one important category of minimally-invasive medicine is optical diagnosis — a suite of techniques that shine light onto tissue to make diagnoses rather than taking invasive surgical tissue biopsies. These technologies hold great promise for diagnostics in obstetrics, ophthalmology, dentistry, gastroenterology and dermatology. CDRH scientists have designed new test methods for evaluating and comparing benefit-risk profiles of optical technologies such as optical coherence tomography (OCT). These methods can help industry to evaluate new devices and provide our reviewers a better foundation to assess safety and effectiveness for new device technologies.

After an approved device has moved to the stage of clinical use, regulatory science plays an important role in developing novel methods to monitor how devices are working in real world patient care. To provide a more comprehensive, up-to-date benefit-risk profile we are developing frameworks that combine data from clinical studies, observational reports and patient registries. In one example, CDRH epidemiologists and statisticians are establishing a computerized safety surveillance system for monitoring adverse event rates of new medical devices. The system has been tested and validated for some interventional cardiology devices, demonstrating that it can detect rates of adverse events above expected levels, and do so more quickly than today's surveillance systems. It is currently being expanded to other products, including hip implants. Data from these activities provides valuable information for device designers and for our own reviewers.

REGULATORY SCIENCE COLLABORATIONS

CDRH has developed synergistic collaborations with other government agencies, academia, industry, and professional societies. This enables us to take advantage of the expertise and resources available in the scientific and medical communities and expands our scientific capability in developing better assessment tools and test methods to assure the safety and effectiveness of medical devices.

We generally engage in these efforts through collaborative agreements and public-private partnerships. CDRH uses Memorandums of Understanding (MOUs) with government agencies such as the Federal Communications Commission (FCC), Centers for Disease Control and Prevention (CDC), and the Department of Defense to share and collaborate on important public health issues. CDRH had 10 active Cooperative Research and Development Agreements (CRADAs) in 2011 with various partners that are advancing regulatory science.

Under one of these CRADAs, we and our collaborators have developed a computational "Virtual Family" of anatomically correct models, consisting of an adult male, an adult female, and two children. These models are used to investigate how various devices interact with the body. This can help speed the design and testing of new and improved devices by allowing developers to test early versions of the device on the computer model instead of on people. This can potentially minimize the risk to patients, speed the development times, and reduce costs.

KEY PRIORITIES IN REGULATORY SCIENCE

CDRH has focused its regulatory science efforts in seven priority areas. Each of these areas is briefly explained on the following pages, along with one or more examples. We provide additional examples in Appendix I.

A. Advancing medical device innovation and evaluating new and emerging technologies;

B. Improving device quality and manufacturing;

C. Analyzing medical device performance;

D. Improving medical device safety;

E. Developing novel ways to use clinical data in evaluating medical devices;

F. Protecting against emerging infectious diseases and terrorism; and

G. Improving the health of pediatric and other special populations.

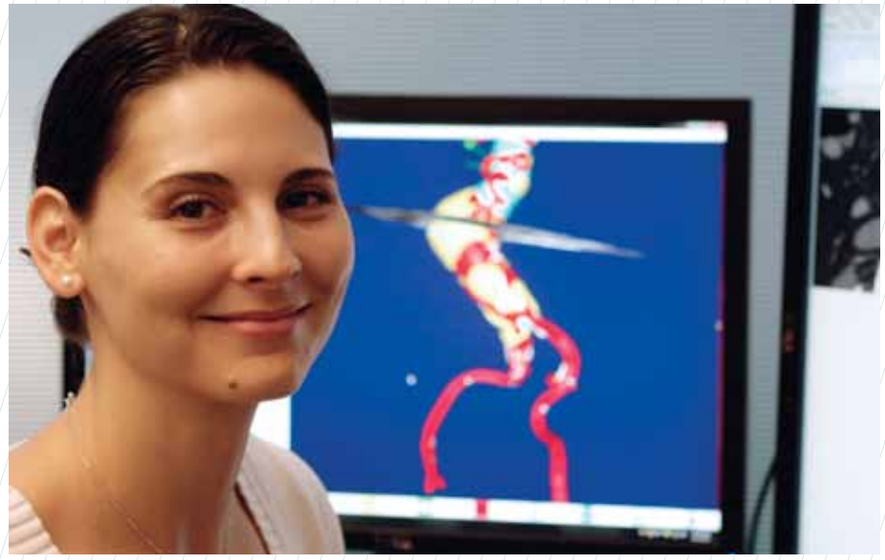
A.
Advancing Medical Device Innovation and Evaluating New and Emerging Technologies

With the very rapid changes in science and technology that are currently taking place, medical devices are becoming more complex and innovative. In order to continue to protect and promote public health, CDRH must anticipate and respond to these changes with state-of-the-art science and sound regulatory decisions.

REVOLUTIONIZING DEVICE DESIGN USING COMPUTATIONAL MODELING

Computational modeling, which uses computer-based mathematical techniques, could revolutionize the field of medical devices by predicting how a device will perform before a single prototype is produced. We're using computational modeling to anticipate the performance of medical devices when they're used in various patient groups, including children and pregnant women. Among the devices we've investigated are cardiovascular devices and innovative medical imaging systems. By providing these new computer models to device designers, we're helping ensure that cutting-edge devices are safe and effective, and that they can reach physicians and patients as quickly as possible. Eventually, physicians may be able to use computer models in personalized medicine, using imaging data to test a device on a virtual patient before it's implanted. [1-8]

Tina Morrison, Ph.D., biomedical engineer
CDRH reviewer, 10 years professional experience.



ASSURING THE ACCURACY OF WHOLE GENOME SEQUENCING

Whole genome sequencing (WGS) is a quick way to analyze a person's entire genome. Until now, WGS has been used primarily in research, but this technique is now nearing clinical use. This could be a significant breakthrough, benefiting patients through vastly improved diagnoses. But before this can happen, we need science-based ways to evaluate the tests and assure that the results are accurate. We're collaborating with other government agencies, academia, and industry to do this.

Elizabeth Mansfield, Ph.D., biologist
CDRH manager, 10 years professional experience.

ENSURING THE SAFETY OF NANOTECHNOLOGY USED IN INNOVATIVE MEDICAL DEVICES

Nanotechnology has the potential to revolutionize medical devices, but there are still important questions to answer. For example, we need to know more about the possible toxicity of nanoparticles and about how to measure their sizes. To help answer these questions, we've been investigating ways to determine the biological effects of nanoparticles and whether current methods can predict these effects. So far, we've developed ways to measure nanoparticle size and uniformity. We've also studied the way tissues respond to nanoparticles compared with larger particles, and we're also looking at the potential toxic and inflammatory effects of nanoparticles. This research will give us a better understanding of the potential safety problems that could affect the development of new medical devices based on this emerging technology. [9-13]

Peter Goering, Ph.D., toxicologist (left)
CDRH researcher, 27 years professional experience.

Brendan Casey, Ph.D., materials scientist (right)
CDRH researcher, 6 years professional experience.

FOSTERING THE DEVELOPMENT OF ULTRASONIC SURGERY

Minimally invasive ultrasonic surgery, which uses high intensity focused ultrasound (HIFU), is a leading-edge technology to perform surgery without incisions. Dozens of efforts are underway around the globe to develop HIFU applications, such as destroying diseased tissue and controlling internal bleeding. But existing methods to test HIFU systems have been complicated and often unreliable. To help manufacturers and developers, we've developed improved test methods for these products and evaluated tests developed by others. We've also provided criteria for developers to determine whether simple calculations will be adequate to provide reliable results for their particular devices. We expect that these efforts will help reduce the number of invasive surgeries that patients need. [14-19]

Gerald Harris, Ph.D., electrical engineer (left)
CDRH researcher, 44 years professional experience.

Subha Maruvada, Ph.D., acoustics (right)
CDRH researcher, 11 years professional experience.

B.
Improving Device Quality and Manufacturing

The safety and effectiveness of medical devices depend on a number of factors, including design, manufacture, quality assurance, packaging, labeling, storage, installation, and servicing. Unlike many other products regulated by the FDA, medical devices often contain hundreds of complex components and systems, all of which must work together. Research in this area focuses on improving the initial product design and manufacturing processes as well as techniques to detect problems when they arise.

REDUCING UNNECESSARY RADIATION EXPOSURE FROM MEDICAL IMAGING

Medical x-rays, including CT scans, are indispensable in diagnosing illness. But it's important to keep patients' radiation exposures as low as possible. To do this, we're working with manufacturers to improve operator information about the radiation dose to be delivered and to alert them in advance about potentially high patient exposures. We're also working on standards for quality control in x-ray facilities and for x-ray operators' qualifications. And we're establishing standards to minimize children's' x-ray exposure. In addition, we're developing computer simulations of x-ray imaging procedures and making them available to academia and industry. These tools allow the designers of medical imaging systems to evaluate innovations in the design phase, so they can quickly assess tradeoffs between image quality and radiation dose. [20]

Kyle Myers, Ph.D., physicist (left)
CDRH researcher, manager, 26 years professional experience.

Stan Stern, Ph.D., physicist (right)
CDRH radiation safety scientist, 29 years professional experience.

c.
Analyzing Medical Device Performance

Once medical devices are on the market, is it important to monitor their performance in order to identify potential problems that could place patients at unnecessary risk and warrant additional mitigations. Such information might also help support future approvals and clearances of new technologies, as well as modifications of existing technologies. CDRH uses a variety of sources to gather and analyze post-market information, and to identify and track trends. Some of these activities are device-specific and others are more general approaches to using the data in quantifying benefits and risks posed to patients from medical devices.

ASSESSING THE STRUCTURAL INTEGRITY OF SPINAL DISC IMPLANTS

Many people with serious back problems affecting the discs between their spinal vertebrae have surgery to replace their diseased disc tissue with an implant that's inserted in the space between the vertebrae. We now know that these devices can fail by pressing against each other and adjacent tissue. That causes pain and excessive wear and sometimes requires surgical replacement of the implant. Traditional ways of testing these products can't identify whether an implant is going to be susceptible to this kind of failure, and so we're working on a new standardized test method that can help predict how strong the implants will be in actual use. We're developing this method by simulating the wear seen in actual use and analyzing failed components. This should help assure that they won't fail in patients.

Jonathan Peck, M.S., mechanical engineer (left)
CDRH reviewer, 8 years professional experience.

Genevieve Hill, B.S., biomedical engineer (right)
CDRH reviewer, 8 years professional experience.

D.
Improving Medical Device Safety

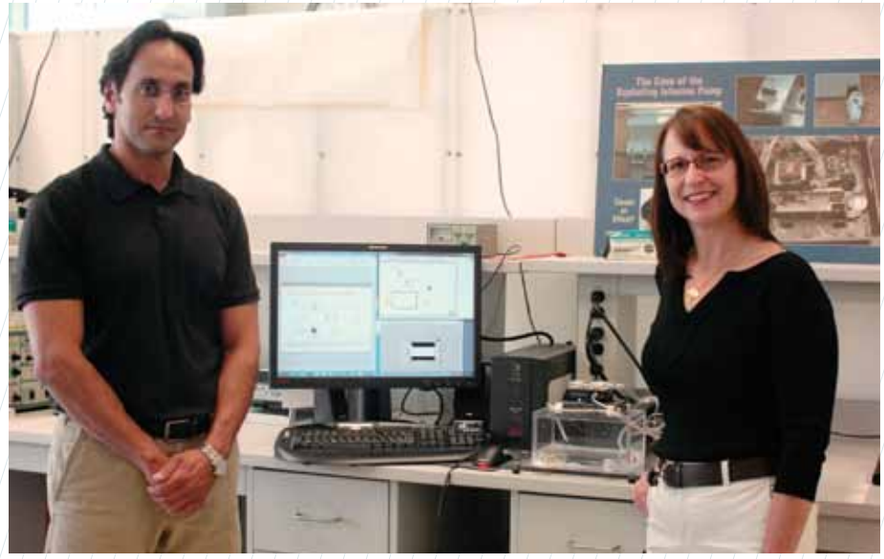
As information accumulates about the safety and effectiveness of medical devices, CDRH is regularly confronted by new safety questions for individual devices and product types. In addition to dealing with these issues as they arise, we are conducting research that will help prevent problems from occurring in the first place or from recurring over time.

ASSURING THAT "SMART" DEVICES ARE RELIABLE

"Smart" software-based devices can adapt to a wide range of patient characteristics and environmental conditions, as well as to changing patterns in patient symptoms. Examples include microprocessor-controlled pacemakers, implanted neurostimulators, and complex imaging systems. These devices depend on thousands (sometimes millions) of lines of complex software code. It's difficult for device manufacturers to evaluate these systems and to detect every possible software glitch that can produce unintended consequences for patients. To address this problem, we've developed techniques to verify the proper functioning of software systems and to detect potentially important flaws. Device manufacturers are already using these methods to make new products safer while reducing development costs. [21]

Hamed Ghods, M.S., electrical engineer (left)
CDRH researcher, 13 years professional experience.

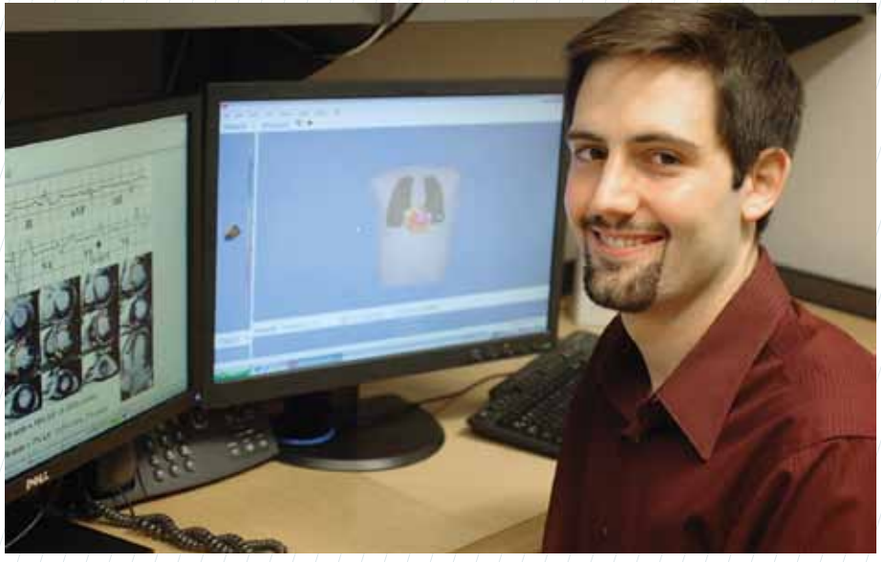
Lisa Simone, Ph.D., biomedical engineer (right)
CDRH researcher, 20 years professional experience.



PREDICTING PATIENT OUTCOMES FROM IMPLANTABLE DEFIBRILLATORS

Implantable cardioverter defibrillators (ICDs) are essential tools in treating abnormal heart rhythms that cause sudden cardiac death. But these devices come with significant risks and can deliver inappropriate and potentially fatal shocks even when there's no actual cardiac emergency. That means it's important to limit implantable defibrillators to patients most likely to benefit from them. Using cardiac MRI data, we've developed a new index of scar formation that's based on the patient's electrocardiogram (ECG) results. We've found that patients without scarring have a high risk of inappropriate shocks. And so we're working on determining whether the ECG scar index can be an effective, non-invasive tool for determining which patients are most likely to benefit from implantable defibrillators, and identifying those that might be at increased risk. [22-24]

David Strauss, M.D., Ph.D., electrophysiology researcher
CDRH researcher, 6 years professional experience.



E.
Developing Novel Ways to Use Clinical Data in Evaluating Medical Devices

In order to help assure the safety and effectiveness of medical devices, CDRH needs reliable ways to acquire and evaluate clinical data on how devices perform, both before and after marketing. Our epidemiologists, statisticians, mathematicians, computer scientists and bioinformaticists work together to identify important public health trends from medical device data. However, the sources of information at our disposal have not always been adequate to provide the needed information. To improve our ability to analyze real-world device performance, we are collaborating in a public-private partnership with clinical experts outside CDRH to develop new ways to find, collect and analyze information on device performance.

CREATING AN EPIDEMIOLOGY NETWORK FOR MEDICAL DEVICES

The clinical studies that are performed before a device is marketed are often limited in size and short-term, and they can't always detect long-term outcomes and rare adverse events. Also, it can be difficult to generalize the results of these studies to the broad range of patients that may use the device after it's marketed. To overcome these limitations, we're developing novel ways to analyze data from diverse data sources. We're collaborating with a professional organization, academic centers, and industry to establish the Medical Device Epidemiology Network (MDEpiNet), a public-private partnership to evaluate clinical evidence and develop new approaches for studying devices in use. The information and methods developed by this partnership will help all of us more accurately determine the benefit-risk profile of devices once they're marketed and used in patient care.

Danica Marinac-Dabic, M.D., Ph.D., physician, epidemiologist
CDRH epidemiologist, manager, 26 years professional experience.

F.

Protecting Against Emerging Infectious Diseases and Terrorism

Infectious diseases are a growing national and international problem, in part due to globalization, the emergence of drug-resistant pathogens, and the threat of bio-terrorism. CDRH is evaluating the effectiveness of devices that can detect, prevent or treat infections and biological threats, or that can destroy pathogens that can contaminate devices. There are also many medical devices used to prevent terrorist attacks and to treat victims, from radiation detectors to biosensors to portable ventilators. CDRH is evaluating and ensuring that these devices are available when needed.

DECONTAMINATING MEDICAL DEVICES EXPOSED TO BIOLOGICAL WARFARE AGENTS

If critical medical devices became exposed to infectious agents during biological warfare and they couldn't be replaced, they'd have to be decontaminated. Anticipating this problem, we're working to be sure that the standard methods for disinfecting devices contaminated with anthrax and *Clostridium* are effective. We're researching how device design affects infection control, and developing methods to test for contaminants in new diagnostic products. This will help safeguard healthcare personnel during emergency situations and help avoid shortages.

Sally Hojvat, Ph.D., biochemist (left)
CDRH reviewer, manager, 38 years professional experience.

Victoria Hitchins, Ph.D., microbiologist (right)
CDRH researcher, 39 years professional experience.

G.
Improving Health of Pediatric and Other Special Populations

Children, women, and persons with disabilities, as well as people who must use complex medical devices at home, have special health needs that may not be adequately addressed using conventional approaches. CDRH is addressing these needs by encouraging innovative approaches to the design of devices used in special circumstances, by making clinical study designs more inclusive of certain populations, and by educating parents and caregivers about using devices.

MONITORING TUMOR RESPONSE DURING BREAST CANCER CHEMOTHERAPY

Current methods for measuring the effect of chemotherapy on breast cancer tissue have often been inadequate to predict how the tumor will respond. To help address this problem, we're developing new analytical tools using multiplex protein arrays that can rapidly monitor tumor response. This will aid in selecting the right drug for the right patient. Our goal is to better personalize breast cancer treatment and reduce the patient's exposure to ineffective and potentially toxic therapies.

Marilyn Lightfoote, M.D., Ph.D., immunologist, allergist (left)
CDRH researcher, manager, 20 years professional experience.

Kim Sapsford, Ph.D., analytical chemist (right)
CDRH researcher, 10 years professional experience.

FUTURE DIRECTIONS

New developments in medical device technology are emerging that will affect the practice of modern medicine and change the nature of patient care. Many new devices will be enabled by major scientific advances. These trends will provide momentum for innovations such as an artificial pancreas, tissue-engineered products, robotic limb prostheses, neurological and neuro-sensory devices, closed-loop, wirelessly-linked, interactive networks of intelligent products, advanced diagnostics, and miniaturized implanted devices based on nanotechnology.

New trends in clinical care will create markets for new technologies. For example, minimally-invasive medicine is driving such developments as percutaneously-deliverable implants, robotic surgical systems, and advanced imaging methods. Similarly, the movement towards decentralized monitoring and care is creating incentives to develop new remote patient monitoring systems, home- and self-care products, wearable diagnostic devices using new types of biosensors, and mobile lab-on-a-chip systems for clinical laboratory tests. And as personalized medicine continues to advance, new assessment tools will be needed, including biomarkers, genomic and proteomic detection arrays, computer-assisted diagnostic tools, and computational models like the virtual patient.

It will be vital for us to keep up with these kinds of changes, and to develop the needed assessment methods. This will enable the deployment of important new technologies quickly and cost-effectively. Additional information regarding future trends in medical devices can be found in Appendix II.

OVERVIEW CONCLUSION

We hope this report provides useful insight into the science that supports our public health mission. Maintaining a strong program of regulatory science in CDRH will enable us to continue to assure the safety and effectiveness of medical devices that can improve the health and enhance the lives of millions of patients. At the same time, it will help us to anticipate and prepare for the emerging technologies that will keep America the leader in medical device innovation, and give the public access to new technologies as they are developed by a robust device industry. Regulatory science will create incentives to innovate by reducing the time and cost of device development, assessment, and manufacturing.

APPENDIX I

Summary of Current Regulatory Science Activities in CDRH

This appendix describes many of the specific projects CDRH has undertaken in regulatory science. They are organized according to the key priorities listed in the body of the report, and in some cases include references for further information. See the Index for a full list of projects.

A.
Advancing Medical Device Innovation and Evaluating New and Emerging Technologies

MEDICAL IMAGING

- **Making Implanted Devices Compatible with MRI**
  Magnetic resonance imaging (MRI) is an important and widely-used diagnostic tool. However, MRI machines can significantly heat or move certain types of implantable devices, and can disrupt implant function. Also, implanted devices may distort the MRI images. For these reasons, patients with some types of implanted devices (e.g., implanted defibrillators and brain stimulators) have not been able to undergo MRI testing, which puts their physicians at a diagnostic disadvantage. To facilitate the development of innovative MRI-compatible implanted devices, CDRH scientists, in collaboration with academia and industry, have performed electromagnetic testing of novel device designs, developed physical and computer models to evaluate them, and established standards for new MRI-compatible devices. This has helped open a scientifically sound pathway for the development of new products, and has led to approval of the first MRI-compatible implantable devices. [1, 25, 26]

- **Assuring Consistency in Novel Medical Imaging Displays**
  X-rays, CT scans, and MRI scans are now being displayed in a variety of ways — in color, 3-D and high resolution, for example. Another new technique is whole-slide imaging, which uses digital images on a computer instead of a microscope to evaluate pathology samples in diagnosing various medical conditions. Until recently, there were no standard requirements for the different ways

to display medical images, or ways to compare results between computers and between facilities. This resulted in inconsistent display characteristics and led to errors in diagnosis. To help deal with this problem, CDRH scientists have developed standardized methods and specifications for assessing medical imaging displays. These methods are now part of an international consensus standard. We are developing similar methods for whole-slide imaging. These efforts will assure that all medical images are displayed according to a basic set of standards, and that radiologists and pathologists are not disadvantaged by poor display technology when they assess scans. [27-32]

- **Advancing Computer Aided Diagnosis (CAD)**
  Computer aided diagnosis (CAD) is now employed in many radiology systems, such as those used to diagnose colon cancer, and will be applicable to other diseases as well. CAD depends upon a complex sequence of instructions and calculations, called algorithms, to characterize radiological data and help clinicians draw conclusions. The algorithms at the core of these devices are modified frequently. Manufacturers and CDRH must evaluate the safety and effectiveness of each change. However, requiring a "reader study," in which a human clinician confirms the reliability of the diagnostic information resulting from every variation, may not always be necessary. CDRH researchers are investigating better ways to do this. We are examining whether machine performance results, combined with the results from original clinician reader studies, can be used to characterize the performance of new device algorithms. This will help ensure that CAD will provide doctors and patients with consistent information while reducing burdensome testing previously required to reach this conclusion. [33-37]

CARDIOVASCULAR DEVICES

- **Improving Clinical Trials for Treatment of Peripheral Vascular Disease**
  Treatment options for some forms of peripheral vascular disease have not been well studied in clinical trials. This includes treatments for critical limb ischemia (CLI), a common yet serious chronic disorder that results in diminished blood flow to the limbs. To help generate additional information about the best way to treat peripheral vascular disease, CDRH has been working with a medical professional society to identify appropriate endpoints and performance goals for prospective clinical trials of CLI treatments. CDRH has also worked with a consortium of cardiologists to analyze clinical data from patients treated with balloon angioplasty (a procedure to open blocked blood vessels) to improve blood flow in the limbs of CLI patients. As a result, several clinical trials involving new stent designs have begun, each following a relatively consistent and standardized approach. Both of these collaborations will improve the design of clinical trials for devices to treat CLI and will ultimately enhance treatment options for patients. [38-41]

- **Improving Graft Technology in the Treatment of Aneurysms**
  Acute aortic aneurysms are characterized by a sudden weakening of blood vessel walls within the chest. They can occur without warning and be fatal, which makes it difficult to conduct design clinical studies to evaluate new types of treatments. CDRH collaborated with professional organizations, manufacturers, and academia to analyze existing clinical data and establish a performance goal for clinical studies of aneurysm grafts used to treat this life-threatening condition. These data, which are now available to any device manufacturer, can help them develop consistent and rigorous controls for clinical trials of devices to treat

aortic aneurism. As a result of this project, several new trials have recently begun, which may lead to improved treatment options for people with aneurysms.

COMPUTATIONAL MODELING

- **Developing a "Virtual Family" to Evaluate Medical Devices**
  Evaluating medical devices using computational modeling has the potential to be more efficient and less expensive than present techniques. But this can only be achieved with multiple computer models that represent the range of the human population. Using a Cooperative Research and Development Agreement (CRADA), CDRH has developed a computational "Virtual Family" consisting of anatomically correct whole body human models of an adult male, an adult female, and two children. The "Virtual Family" models are based on high resolution MRI scans of healthy volunteers and include more than 80 different tissue types. They enable us to investigate how a broad range of devices interact within the body. We have already used the Virtual Family to study the temperatures around implanted devices when human bodies are exposed to radiofrequency and microwave radiation. The techniques and tools developed in this study can be used to help us develop future models and improve the accuracy of the models so that they can be applied to a broader range of devices. [42]

- **Establishing a High-Performance Computer Facility**
  Engineering analysis methods are needed to predict whether a proposed medical device design will function properly and safely. Computational modeling methods can help provide this information by integrating data from a variety of sources (animal, preclinical and clinical). To facilitate the development of computational modeling, CDRH engineers have established a high-performance computer facility to develop models for emerging device technologies. Other applications for use have already included high intensity focused ultrasound designs, deep brain stimulators, optical diagnostic techniques, and bone densitometry methods.

BIOMARKERS AND PERSONALIZED MEDICINE

- **Standardizing Brain fMRI as a Biomarker in Clinical Trials**
  Measurements of biomarkers are used to indicate the presence of underlying disease states. Many biomarkers are biochemical in nature (such as proteins or genes), but other tests, including imaging, can also be used as biomarkers. For example, functional MRI (fMRI) is a popular, non-invasive method used in clinical trials to assess the safety and effectiveness of new medical devices and drugs by measuring changes in brain activation. It has especially great potential in selecting patients for different types of neurological treatments. Unfortunately, there is presently no standardization in how fMRI is used, and results vary with different techniques. This variability makes it difficult to use the measurements in evaluating new products. CDRH researchers are developing standardized methods for the use of fMRI in clinical trials, which will make it more effective in the pre-market evaluation of new neurological devices. [43]

- **Assuring the Reliability of Troponin Tests in Detecting Heart Attacks**
  It is sometimes difficult to determine whether a patient with chest pain is having a heart attack (also known as a myocardial infarction or MI). Although cardiac troponin has become increasingly valuable as a biomarker to detect MI, many older troponin tests may not be able to detect low enough concentrations of troponin to diagnose MI reliably. To address these issues, CDRH is working with troponin assay manufacturers to modernize methods for evaluating

their products, and is identifying the data needed to evaluate whether a troponin test is capable of detecting low concentrations of troponin. [44]

- **Developing a New ECG-Based Biomarker to Help Diagnose Heart Failure**
  In diagnosing and treating heart failure, a condition in which the heart no longer efficiently pumps blood, it is important to quickly measure rapid changes in cardiac output. CDRH is working on a new biomarker that could achieve this goal. CDRH scientists have developed a model for evaluating blood flow in the heart based on certain characteristics of the ECG. We are now at the stage of comparing laboratory measurements of cardiac blood flow with measurements in human subjects. When completed, the new biomarker will increase patient safety during clinical trials, and could also be used widely in clinical practice to measure heart failure more quickly. [45]

- **Finding Novel Biomarkers for Kidney Disease and Renal Failure**
  The traditional biomarkers used to detect acute kidney injury have been too insensitive to detect injury before a substantial amount of harm occurred. CDRH has developed new, more sensitive biomarkers that will detect kidney injury before serious damage occurs. The new biomarkers are being studied in the following areas: (1) identifying the concentration of chromium associated with kidney damage, which is important for patients with metal-on-metal orthopedic implants; (2) evaluating the extent of kidney injury associated with the food contaminant melamine in collaboration with FDA's National Center for Toxicological Research (NCTR); and (3) measuring free hemoglobin that could damage the kidney, which is important for patients on cardiopulmonary bypass. This work has also spurred the development of a new "renal injury" cDNA chip which can assess changes in genes associated with kidney injury. This could replace current screening methods that rely on expensive microarray chips, thus decreasing health care costs and improving detection of kidney injury. [46]

- **Improving the Detection of Chromosome Defects**
  Many human genetic disorders, which can result in congenital anomalies or developmental disabilities, are a result of gross chromosomal anomalies. The recent development of new methodologies for analyzing DNA (array cytogenetic methodologies) has created a better method of evaluating these chromosome abnormalities. These tests are currently being used to look at the patient's entire genome instead of focusing on a specific disease or syndrome, which could miss other abnormalities. CDRH is working with experts in the field to develop ways to validate the effectiveness of these tests and their results, as well as to determine what kind of special controls, if any, are needed to assure that the tests can be used safely and effectively.

REGENERATIVE MEDICINE AND NEW MATERIALS

- **Unlocking the Promise of Tissue Engineering and Regenerative Medicine**
  Cartilage cells called chondrocytes are used extensively in tissue-engineered combination products that can regenerate or replace a variety of tissues, including cartilage. A major obstacle in this type of therapy is that current laboratory techniques for growing chondrocytes can cause these cells to develop different characteristics than they have in their natural environment. CDRH scientists are working with other FDA Centers and academic collaborators to develop tests to assure that chondrocytes will maintain their normal characteristics

while being grown in laboratories. This work will enhance the availability of chondrocytes and help in the development of new types of tissue-engineered products.

- **Forging the Way for the Use of New Reabsorbable Biomaterials in Medical Devices**
  Manufacturers are currently developing cardiovascular stents designed to be absorbed into the body after they have reduced blood vessel blockages. To help assure the safety and effectiveness of these stents, CDRH is researching methods for measuring the mechanical forces on the stent and its degradation in the body. Using this information, CDRH is developing standardized test methods that manufacturers can use in developing these devices. This work may also apply to other new absorbable medical devices such as orthopedic and dental products.

- **Addressing the Toxicity of New Materials**
  Prior to marketing a new device that will come in contact with the fluid around and inside the brain and spinal cord, the manufacturer must perform tests to be sure that the device will not be toxic to the central nervous system. These devices include those intended to treat Parkinson's disease as well as blood clots affecting the nerves. In cooperation with a national standards group, CDRH has developed a new standard test method to guide manufacturers in performing these tests. The standard should help bring important new neurological devices to market more quickly. It should also decrease the number of adverse events in these devices once they are marketed. [47]

OPHTHALMIC DEVICES

- **Facilitating the Next Generation of Intraocular Lenses**
  Intraocular lenses (IOLs) are minimally invasive implants that are used to replace the lens in the eye. They are widely used in cataract surgery and other eye procedures, and they remain a rapidly evolving medical device technology. IOLs have posed challenging measurement and testing problems since the first simple designs came into use. Recent developments in IOL design have brought new performance problems, which were discovered and analyzed in CDRH labs, such as unintended reflections inside the eye and cavities in some of the lenses. Further, new designs have resulted in lenses with a much wider range of optical powers that have outstripped the original quantitative tests. CDRH scientists have used modern fiber optic techniques to create new test methods to accommodate these newer products. These CDRH-developed tests have once again become the prevailing industry standard. This work has enabled the Center to effectively evaluate new generations of IOLs and forestalled widespread vision problems resulting from lens problems. [48-51]

- **Paving the Way for Retinal Prostheses**
  Significant progress has been made in developing retinal prostheses for the blind, but important challenges remain in developing a clinically effective device. CDRH scientists are helping address these challenges by analyzing how stimulation of the retina affects the light-evoked responses of the retinal cells. We have also generated animal and bench methods to test the safety and effectiveness of retinal prostheses as these innovative devices are being developed. By clarifying how the signals from electrodes affect living nerve cells in the patient's retina, this work is helping to overcome the barriers that have thus far hindered these breakthrough devices from reaching the visually impaired people who need them. [52-54]

MINIMALLY INVASIVE DEVICES

- **Facilitating the Development of Optical Diagnosis**
  New technologies are allowing the development of medical devices for minimally invasive diagnosis and therapy. These technologies can reduce patient trauma and recovery times and reduce healthcare costs. One of these is optical diagnosis, which employs various wavelengths of light to identify abnormalities in many types of tissues. Optical coherence tomography (OCT), a type of optical diagnosis, is an expanding technology capable of producing minimally invasive, cross-sectional images of tissue with very high resolution. OCT is already being used in ophthalmology to examine the retina and cornea, and, in combination with endoscopy, in cardiovascular medicine. New applications for OCT are presently being developed in other areas, such as dentistry and dermatology. To help hasten the progress of this promising technology, CDRH scientists have designed new test methods that can be used to evaluate and compare OCT devices. These methods will facilitate the development and approval of new medical devices that can make better and more accurate medical diagnoses. [55]

INNOVATIVE HORIZONS

- **Surmounting the Technological Barriers to Creating the First Artificial Pancreas**
  Diabetes affects more than 23 million people in the United States and contributes to approximately 170 billion dollars in health care costs every year. Controlling diabetes is difficult, as it requires frequent measurements of blood glucose and constant insulin dose adjustments. An artificial implanted pancreas, if it could be developed, has the potential to overcome these problems and significantly improve the lives of diabetic patients. It is intended to be an autonomous (self-controlling) system in which a device that monitors glucose levels feeds information to an implanted insulin pump via computer software. CDRH has worked with other Federal agencies and outside groups on ways to overcome the scientific obstacles in developing an artificial pancreas and to establish reasonable clinical expectations for these systems. We are helping researchers and industry to focus their efforts by providing a transparent and predictable regulatory path forward in developing an artificial pancreas. Thus far, we have developed tools to facilitate research, such as approving a computer model that eliminated the need to conduct animal testing. CDRH researchers will continue to develop new tools to evaluate these innovative devices. [56, 57]

- **Assuring the Safety of Medical Robots**
  The use of robotics in medical applications is rapidly growing in scope and complexity. Robotic systems are being used in an increasing number of surgical applications, as well as in augmentation of therapy in rehabilitation settings, replacement of musculoskeletal and cognitive function, and individualized medical care. Further, there are new applications of intelligent machines for diagnostic purposes and for enhanced processing of biological tissues. The ongoing development of new robotic systems and applications for use in medicine presents unique challenges for industry and regulatory agencies. CDRH engineers have been analyzing robotic medical systems to identify intrinsic failure modes and the performance characteristics of these systems. They are also developing tools for the evaluation of the software controllers employed by robotic systems. Using this and other information, CDRH is working with an international standards development committee to address the safe design of personal care and medical robots that are designed to collaborate with humans. These standards will define specific ways to minimize risks so as to enhance the safety of these devices.

Robotic systems to evaluate device performance

B.
Improving Device Quality and Manufacturing

MANUFACTURING AND QUALITY

- **Improving the Engineering Design of Infusion Pumps**
  Based on a postmarket analysis of performance problems, along with data from manufacturers, users and patients, CDRH has undertaken an in-depth evaluation of external infusion pumps—devices that deliver fluids, including medications and nutrients, into a patient's body. Historically, these products have been responsible for a disproportionate share of adverse events and recalls. Our evaluation has identified systemic deficiencies in the way infusion pumps are designed, manufactured, and reviewed. For example, design defects may occur in software, hardware (mechanical or electrical), or user interface design. Based on a retrospective study of these defects, CDRH was able to generate a list of hazards that may present a risk to health. This list was used to give guidance to manufacturers on providing detailed design and engineering information and on providing the results of validation testing, with special emphasis on human factors testing. Manufacturers must also present a safety assurance case report, which provides a structured set of arguments for how the pump hazards have been addressed. The guidance also specifies the data that should be included in adverse event reports, and recommends the type of information that should be given to caregivers concerning safe use of the pumps. This data will help CDRH researchers in the future as they analyze the reports to detect problems in the future. [58, 59]

- **Identifying Emerging Product Safety Issues**
  When a product defect or manufacturing problem is identified, CDRH researches the root cause of the failure and how it might affect performance, and develops a risk-assessment of the issue. A recent example of this type of root cause analysis involved Huber needles. These needles are used to access silicone ports implanted under the skin of chronically ill patients for repeated access to veins to withdraw blood and deliver medications. Adverse events associated with Huber needles were detected by CDRH's Medical Product Safety Network (MedSun), a reporting program that works with the clinical community to identify and solve problems with the use of medical devices. FDA field inspection reports revealed that these needles may cut and dislodge silicone slivers from the ports into which they are inserted, resulting in potential leakage and hazards to the patient. CDRH developed reliable test methods, evaluated the products, and identified the causes of the problems. This resulted in a public health notification and a Class I recall of more than 2 million Huber needles. The CDRH-generated test methods are now being used by manufacturers during needle design and production. [60]

- **Preventing Infections from Reusable Devices**
  Reusable devices, such as forceps, endoscopes, and stethoscopes, must undergo reprocessing, a multi-step process to clean, disinfect, or sterilize them. Inadequate reprocessing can result in blood, tissue, or other biological debris remaining on the device, which can cause infections. CDRH is investigating computational modeling to study fluid flow and debris on devices. We are also working with other Federal agencies, industry and academia on ways to improve the design of reusable devices so that less debris will remain on them after use. These efforts will help manufacturers design better reusable devices and reduce health-care associated infections in patients. [61]

- **Analyzing Failures of Defibrillator Leads**
  If the leads (connecting wires) on an implantable defibrillator (ICD) fail, this can result in loss of pacing, loss of shocks, or painful, inappropriate shocks, which may induce dangerous arrhythmias and death. CDRH is collaborating with the Department of Veterans Affairs in an epidemiological study of a large patient population to determine the rate at which these leads fail, and the causes of failure. Using conclusions from this research, we will work with defibrillator manufacturers to help them produce more reliable ICDs that can reduce adverse events to patients.

Engineering safety evaluation of patient cables

- **Making Device Labeling More Accessible**
  CDRH-approved labeling for medical devices includes important information such as indications for use, operational instructions, warnings and precautions, and basic maintenance and cleaning. At present, it can be difficult for users of medical devices to readily find this information. The version of the device that the patient uses may have been discontinued or the device may have been changed since the patient received it, and information on older models can be hard to find. Or the labeling may have been given to the healthcare provider rather than the patient, as with implantable medical devices, and patients may have no central place to find that information. CDRH is researching the possibility of developing a medical device labeling repository that would be accessible to the public, similar to the drug labeling repository now available on the National Library of Medicine's website. The repository would eventually cover all classes of devices and would provide "one-stop shopping" for anyone who wants to look up what types of devices are available for their medical condition. It would also assist health care professionals to access labeling that may not always accompany a medical device. An important part of this effort is careful social science research into how patients' best receive and use medical information. CDRH is collaborating on research that measures the ability of consumers to comprehend and use the information in device labeling. [62]

- **Preventing Dangerous Misconnections Between Medical Devices**
  Critically ill patients often have many sets of tubing delivering many different types of therapies at any one time. Examples include feeding tubes carrying nutrition into the stomach, intravenous (IV) tube carrying medications into the bloodstream, tracheotomy tubes carrying oxygen to the lungs, and drainage tubes removing urine and waste from the patient. Small bore connectors are widely used on a variety of tubing sets, solution bags and other medical products. Because these connectors are similar and easy to attach to one another, users can inadvertently misconnect them, leading to serious adverse events and death. This is especially problematic among children, where the tubing is often very small. For example, feeding tubes have been mistakenly connected to infant tracheotomy tubes, delivering infant formula into the baby's lungs. Misconnections may be minimized by designing equipment that is color-coded, providing alarms to warn of misconnections, and establishing standard nursing work practices that require checking and re-checking connections. CDRH is chairing an international expert working group that is developing criteria for safe and interoperable small-bore connectors for medical devices. CDRH scientists are providing essential technical leadership for the working group's efforts. [63-65]

c.
Analyzing Medical Device Performance

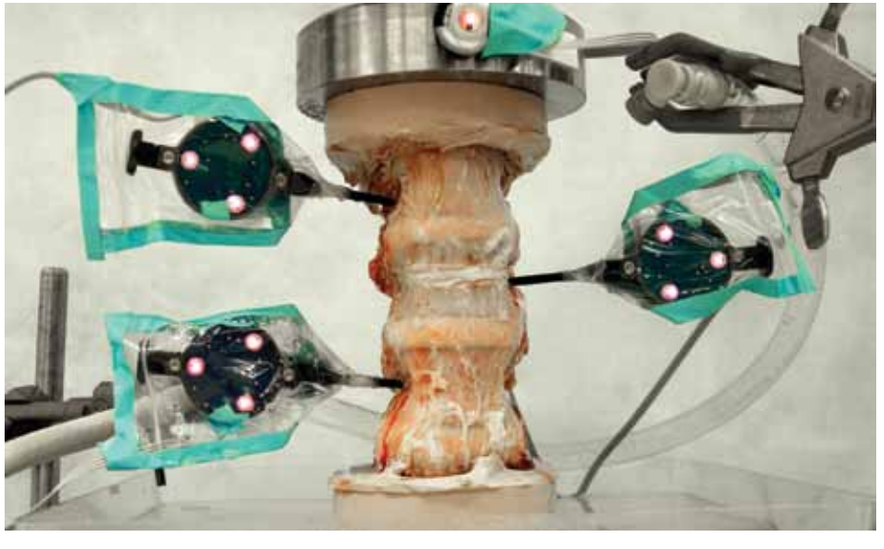
DEVICE PERFORMANCE

- **Improving the Reliability of Cochlear Implants**
  CDRH has received many reports of failures and reliability problems with cochlear implants, which are used to treat severe hearing impairments. In particular, there have been significant problems with leakage in the device's implanted receiver. More recently, there have been poorly understood problems with internal electrical short circuits inside the implant. These problems can have consequences for patients, including pain and loud pops—all of which can require additional major surgery to replace the implant. To help deal with these issues and provide patients with more reliable devices, CDRH scientists, in collaboration with academia, are working to develop methods that can better characterize patterns of device failure, and do so earlier in the development of the product. Additionally, CDRH is working to develop more rigorous laboratory studies which can detect problems with cochlear implant leakage before these devices reach the market. [66]

- **Improving the Way Glucose Monitors Are Used**
  Glucose monitoring devices are crucial in the management of diabetes, a critical and growing public health concern. In response to a number of reports of accuracy and reliability problems with glucose monitors, CDRH scientists evaluated the potential for measurement errors in multiple types of these devices. We assessed the effects of certain non-glucose sugars, which are commonly used in sugar substitutes, medications and dietary supplements, on various kinds of glucose meters, and found that certain types of meters would give erroneously high glucose readings in the presence of these sugars. These findings played a central role in the subsequent issuance of an FDA notification to healthcare professionals, alerting them about this problem and thus contributing to more effective use of glucose monitors and better diabetes care. [67]

PATIENT SUB-POPULATION RESPONSE TO TREATMENT

- **Determining Patient Response to Disc Replacement**
  Artificial disc replacement to treat diseases of the lumbar spine is becoming more widespread due to the aging of the US population. CDRH is working with the National Institutes of Health (NIH) to develop a statistical model that can predict which patient groups are likely to benefit from artificial vertebral disc replacement. Using the model can prevent unnecessary invasive surgery in many patients and reduce healthcare costs. This type of model could potentially be used to predict success with other medical devices.



Investigating factors affecting vertebral device performance

- **Characterizing Quality of Life after LASIK**
  LASIK is a surgical procedure intended to change the eye's ability to focus and thus improve a person's vision. CDRH is working with NIH and the Department of Defense (DOD) on a study to characterize those patients who have significant functional limitations after LASIK surgery. This will help identify sub-populations for whom LASIK procedures may entail increased risk, thus improving outcomes for the overall patient population. [68]

DIAGNOSTICS

- **Making Better Information Available to Users of Diagnostic Tests**
  In the past, manufacturers have sometimes used inappropriate statistical methods to estimate the performance of new diagnostic tests, which can lead to unreliable or misleading test results. CDRH statisticians have developed new, scientifically validated methods for characterizing the performance of diagnostic tests. Based on this work, CDRH issued guidance to manufacturers on how to analyze studies of their devices and accurately report them to healthcare providers and patients, so that diagnostic test results can be interpreted safely and correctly. [69]

- **Assuring that Microarray Gene Technology is Reliable in Predicting Patient Outcomes**
  The use of microarray technology, a method to quickly sample a large number of genes, may lead to tests that can help select optimum treatments for individual patients. However, if the microarray technology is not adequately validated to ensure accuracy, patients could receive incorrect treatments. CDRH statisticians are evaluating common methods for validating microarray technologies to predict patient outcomes. Thus far, we have evaluated the ability of manufacturers to validate the performance of their microarray technologies in treating breast cancer, multiple myeloma, and neuroblastoma. These efforts have identified ways to sharpen the evaluation of microarray technologies, which should increase the reliability of this new medical tool. [70, 71]

D.
Improving Medical Device Safety

ORTHOPEDICS

- **Evaluating the Safety of Metal on Metal Implants**
  In metal-on-metal (MoM) hip replacements, both the ball and the socket of the joint are made of metallic materials. Over time, tiny metal particles from MoM hip replacement implants can wear off of the device and enter the space around the implant, causing damage to bone and other tissue. This can require surgical replacement of the implant. Metal ions from the implant may also enter the patient's bloodstream. CDRH is conducting a comprehensive review of benefit-risk profiles for these implants. This includes assessing utilization trends, patient selection criteria, pre-operative patient counseling, surgical technique, and follow-up and surgical replacement rates. CDRH is studying MoM devices to help understand how and why certain implants fail over time. This information will help CDRH and practicing physicians to better weigh the benefits and risks of these implants. [72]

- **Studying the Performance of Joint Replacement Devices**
  To help study approved orthopedic medical devices, CDRH has collaborated with a major insurance provider to produce valid estimates of problems and adverse events from artificial joint replacement devices. Data gathered from this effort are being analyzed to help us better understand how these devices are used and how they perform, including how device design, surgical technique and patient characteristics affect device safety.

OPHTHALMOLOGY

- **Minimizing Serious After-Effects from Cataract Surgery**
  In recent years, there have been several outbreaks of Toxic Anterior Segment Syndrome (TASS), a non-infectious eye inflammation that can occur after cataract surgery and can lead to glaucoma and damage to the cornea and retina. There is no standardized test methodology to determine a root cause for TASS and no single laboratory capable of assessing products that could potentially cause TASS. In an effort to address these concerns, CDRH has developed a Proactive TASS Program (PTP). Our research is presently assessing whether and how potential contaminants in ophthalmic devices may cause inflammation and contribute to TASS. We are also developing test methods to determine the levels of contaminants that can trigger a TASS reaction. Results from this research are helping CDRH develop a new international standard for certain contaminant levels in ophthalmic devices. CDRH has established the only laboratory in the United States to perform this testing. PTP will enable us to minimize future TASS outbreaks by detecting early signals of an epidemic, identifying the source, and taking appropriate actions.

- **Reducing Infections from Contact Lenses and Lens Solutions**
  Outbreaks of eye infections have been a long-standing problem with contact lenses, which are used regularly by millions of people. In one recent case, blindness-inducing infections occurred in two independent outbreaks in association with contact lens solutions. These incidents led to substantial product recalls. CDRH lab investigations revealed the cause to be a previously unrecognized incompatibility between some contact lenses and contact lens solutions. CDRH scientists then developed new, more effective tests to identify potentially problematic

combinations of lens materials and solutions. This method has been provided to industry and academia to aid in their testing of new lens and cleaning solution products. The results of these studies will also be incorporated in standards and guidance for improved pre-market testing and evaluation of contact lenses and care products. [73]

MEDICAL IMAGING

- **Reducing Errors During Radiation Therapy**
  There have been a number of events in recent years in which patients undergoing radiation therapy unintentionally received very large radiation doses. To help avoid such accidents and improve the safety of radiation therapy, CDRH has undertaken a number of technical and regulatory initiatives. CDRH engineers have conducted independent failure investigations to identify the root causes of radiation over-exposure, and these findings have been used to inform and guide corrective actions and preventive measures. CDRH is clarifying the data needed to approve radiation therapy treatment planning systems, and is working on improved methods to collect adverse event information. These efforts will help healthcare professionals deliver radiation treatment plans as intended and reduce the likelihood of errors.

- **Comparing the Image Quality and Dose of CT vs. Tomosynthesis**
  Although CT scans are invaluable in the diagnosis and treatment of many medical conditions, they have increased population exposure to ionizing radiation. CDRH is collaborating with the Walter Reed National Military Medical Center and academia to investigate whether tomosynthesis, a low dosage imaging modality, can achieve an image quality equivalent to a CT scan. If this proves true, it could lead to a substantial reduction in radiation exposure to the population.

- **Improving Imaging for Lung Cancer**
  Computed tomography (CT) is increasingly being used to evaluate the effect of lung cancer treatments, especially in monitoring the size of tumors. CDRH has produced a publicly available database of CT images of tumor nodules that will help device manufacturers create software that can better estimate tumor size. This database is already being used to assess how the settings on the CT machine affect tumor volume measurement. Ultimately, it will help physicians to better determine whether lung cancer therapies are working, and lead to more personalized and appropriate treatment. [74-76]

DEVICE COMPATIBILITY

- **Assuring the Interoperability of New Interactive Medical Devices**
  "Intelligent" medical devices that can communicate with other devices are beginning to be developed. Although these multi-device systems promise to bring clinical benefits, they might have compatibility problems that could cause them to behave in unexpected ways. CDRH engineers are at the leading edge of this emerging technology. We are identifying the issues as they unfold, establishing venues for initial community dialogue, and creating tools that can help assure system safety. In one example, CDRH co-sponsored a strategic workshop that brought together industry, academia and Federal agencies, and resulted in identifying new research topics and stimulating new research collaborations. As this technology develops, CDRH will work with the medical community to incorporate safety strategies at the very beginning. [77]

- **Reducing Electromagnetic Interference with Implanted Medical Devices**
  Radiofrequency wireless systems, such as those used in toll booths and store price tag readers, are becoming more and more widespread. This raises questions about whether they can interfere with implanted medical devices that contain low-powered electronics. CDRH engineers are testing the susceptibility of these implanted devices to various patterns of electromagnetic radiation. For example, we have evaluated possible interference by metal detectors with implanted neurostimulators. Similarly, we have measured interference with cardiac pacemakers and implantable defibrillators caused by radiofrequency identification (RFID) systems. Based on public concern, we also studied the possible interaction between portable entertainment electronics and cardiac pacemakers, and found no interference problems. CDRH has worked with device manufacturers to find ways to identify and mitigate interference problems. These efforts will help assure that present and future electronic medical systems will be able to operate without interference from electromagnetic radiation in our increasingly wireless environment. [78-80]

Testing medical implants for susceptibility to radiofrequency interference

HOME HEALTH CARE

- **Producing Safer Medical Devices through Human Factors Engineering**
  In the design of medical devices, Human Factors Engineering (HFE) combines behavioral science and engineering to help ensure that the product can be used safely by healthcare professionals and patients. Using HFE can help reduce use error, enhance patient and user safety, improve product usability and efficiency, and enhance user satisfaction. To address these issues, CDRH has established a new Functional Performance and Device Use Laboratory to support research on human factors issues in medical device use. Currently, we are evaluating the potential for speech output to reduce infusion pump programming errors, and we are developing methods to predict a user's ability to operate the manual controls on medical devices. This research will help us understand how environmental conditions, user characteristics, and device features can be improved to reduce device use errors and improve patient outcomes. CDRH has also developed a Human Factors Engineering standard for manufacturers to use in designing their devices and recently issued updated guidance on using human factors in medical device design. [81-83]

ANESTHESIOLOGY

- **Using Simulations to Improve the Reliability of Anesthesiology Devices**
  Drug delivery devices that function semi-autonomously are being developed to monitor patients and deliver anesthesiology drugs. If successful, they could reduce human errors and cut health care costs by decreasing the need for medical practitioners to actively monitor patients. During

research studies, some of these products have malfunctioned, delivering drugs in error. To help identify potential sources of failure in these devices, CDRH constructed a computer model to characterize the problems and identify design changes that might prevent them. The modeling effort is based on a systems analysis of the interaction between the user and the machine. We are also working to evaluate the system software and the susceptibility of anesthesia devices to electromagnetic interference from wireless systems. These efforts will help to assure that patients are protected against possible malfunctions during use.

E.
Developing Novel Ways to Use Clinical Data in Evaluating Medical Devices

STATISTICS

- **Employing Innovative Statistics to Facilitate Medical Device Clinical Trial Design**
  Clinical trial designs and statistical analyses that make optimum use of data from previous trials can lead to more rapid accumulation of safety and effectiveness evidence. As a result, effective technologies can be brought to market faster, and ineffective or potentially unsafe ones can be detected earlier. Bayesian statistics is an approach for learning from evidence as it accumulates. Using Bayesian statistics can permit the enrollment of fewer patients in a clinical trial and can result in new devices entering the market more quickly and efficiently. To facilitate more efficient clinical trial design, CDRH has also entered into a Cooperative Research and Development Agreement (CRADA) with industry to develop software that will assist in the design of Bayesian clinical trials. [84]

- **Using Quantitative Decision Analysis to Evaluate Risk**
  CDRH is exploring the use of quantitative decision analysis to help us make better regulatory decisions. This statistical research method may enable us to quantify benefits and risks for medical devices in an explicit and consistent way both before and after they are marketed. It can characterize and clarify any bias and uncertainty in our decision-making. Quantitative Decision Analysis can also enhance our effort to be transparent to the public regarding our regulatory decisions, and to provide information that will help individuals make important healthcare decisions. It may also give CDRH a reliable mechanism for incorporating patients' views on benefits vs. risks into our assessment of clinical trial data. [85]

DATA UTILIZATION

- **Using Data Mining to Identify Medical Device Problems**
  Adverse events with medical devices are often under-reported by users and sometimes over-reported (during periods of intense news media publicity, for example). The reports we do receive frequently contain incomplete or confusing information, including variations in the product's name. This makes it difficult for us to identify and characterize potential safety issues with devices, and to distinguish "signals" (i.e. significant events) from "noise" in the vast number of reports we receive. By "mining" these various data sources, CDRH can identify signals that might indicate widespread problems affecting a particular device or device type. However, the number of relevant documents that must be checked can be dauntingly large and is increasing rapidly. To address this problem, CDRH is developing a semantic text mining system which can extract and analyze the narrative text in large numbers of electronic documents. Using these techniques, CDRH is building a computerized search, retrieval, and analysis system that can quickly and systematically extract information from a broad range of documents. This will improve our ability to detect trends in device performance before they lead to far-reaching problems that can compromise patient safety.

- **Combining Existing Information to Better Evaluate Devices**
  Addressing premarket and postmarket safety and effectiveness questions about medical devices could be substantially improved if CDRH had a way to combine data from a variety of available sources. To address this problem, CDRH has begun developing a Formal Evidence Synthesis Framework that combines existing data sources, including clinical trials, observational studies, patient registries, published literature, administrative claims data, and other known data sources. This framework will allow CDRH to have a comprehensive, up-to-date benefit-risk profile for a specific medical device at any point in its life cycle, thus enabling us to make optimally informed decisions and provide more useful information to practitioners, patients, and industry. [86, 87]

- **Studying Medical Devices Using Medicare and Medicaid Data**
  CDRH is pilot testing the effectiveness of using Medicare and Medicaid claims data to assess device performance under the FDA's Sentinel Initiative, which uses large, population-based data sources for surveillance of medical products. Device applications in the pilot test have included the use of surgical mesh in pelvic organ prolapse, lap bands to treat obesity, cardiac resynchronization therapy, negative pressure wound therapy, and pediatric intraocular lenses. These pilot studies have thus far demonstrated the usefulness of the claims data and are already influencing the way we conduct medical device surveillance.

- **Applying Comparative Effectiveness Research to Medical Devices**
  Knowing which devices are most effective in a particular type of patient, or conversely, which devices should not be used due to safety concerns, is an important component of CDRH's public health mission and an important component of personalized medicine. To help acquire this information, CDRH is collaborating with the other FDA centers in the Partnerships in Applied Comparative Effectiveness Science (PACES) Initiative, which collects and analyzes data from multiple sources to assess the comparative effectiveness of medical therapies. By combining many studies in a particular area, we may be able to identify patient groups likely to benefit from treatment and those most at risk. In CDRH's portion of this project, we are studying artificial spinal discs, cardiac resynchronization therapy, and continuous glucose monitors.

POSTMARKET SURVEILLANCE

- **Using Registries to Monitor the Use of Medical Devices**
  In order to identify uncommon adverse events associated with medical devices, large populations of patients are needed. To help get this information, CDRH uses patient registries to collect data on large numbers of people treated with a device. Registries can also help assess how devices are used in the real world and what happens to the patients who receive them, allowing us to identify sub-groups of patients who may be at increased risk of adverse effects. CDRH has helped to establish registries such as the Improving Pediatric and Adult Congenital Treatment (IMPACT) registry. CDRH has been able to take advantage of existing registries for cardiovascular, bariatric, orthopedic, and chest surgery data, which we have used in post-market device monitoring. We have also helped establish the International Consortium of Orthopedic Registries (ICOR). In addition, we have used the National Electronic Injury Surveillance System All Injury Program database to characterize emergency department visits for adverse events from medical devices in children. [88-90]

- **Advancing Active Surveillance of Implanted Devices**
  With thousands of Americans receiving medical device implants each year, it is important to be able to identify increased rates of adverse events as they occur. In collaboration with a clinical center and an insurance provider, CDRH is establishing an active safety surveillance system for interventional cardiovascular devices and hip implants called the Data Extraction and Longitudinal Time Analysis (DELTA). DELTA is a computerized tool that can monitor the adverse event rates of newly implanted medical devices using various data sources via automated analytic methods. The DELTA system has been tested and validated for interventional cardiology devices using registry-based data sources, demonstrating that it can detect rates of adverse events above expected levels. DELTA offers a valuable complementary approach to existing methods for medical device safety surveillance.

- **Evaluating the Use of Surgical Mesh in Gynecology**
  The use of surgical mesh to repair pelvic organ prolapse and stress urinary incontinence has increased in recent years—approximately 560,000 procedures are now performed annually in the U.S. As with all surgical procedures, implanting the mesh can result in serious medical complications, and so it is important to evaluate the relative safety of various mesh designs. But that is difficult because it is hard to distinguish between the effects of the mesh itself and the wide range of surgical procedures in which it's used. CDRH is exploring the use of Medicare data, along with other information, to analyze patient outcomes. This will help us identify which combinations of mesh types and surgical techniques provide the greatest benefit to women. [91-93]

Analyzing data on device performance

F.

Protecting Against Emerging Infectious Diseases and Terrorism

H1N1

- **Diagnosing Influenza Rapidly Using Molecular Diagnostic Assays**
  Diagnosing influenza quickly can be critical for patient care. Molecular diagnostic methods to detect influenza, which are more sensitive, robust and rapid than conventional methods, are increasingly being used in clinical practice. CDRH is working with FDA's Center for Biologics Evaluation and Research (CBER) and industry to determine whether one of these methods, detecting viral nucleic acid in a nasal swab sample, is a reliable way to identify whether the patient is infected with influenza virus.

MEDICAL COUNTERMEASURES

- **Cleaning Used Masks During Pandemic-Induced Shortages**
  In the event of a pandemic influenza outbreak, there is a potential for shortages of disposable respirators. Based on recommendations from the Institute of Medicine, CDRH worked with other Federal agencies, universities and medical centers to develop methods for decontaminating single-use, disposable masks so that they might be used again. Masks were exposed to surrogate agents and then to H1N1. Some of the masks showed a decrease in the virus after decontamination using these methods, showing that it might be feasible to re-use disposable masks during a pandemic.

- **Dealing with Bacterial Contamination of Medical Devices**
  Bacterial pathogens constitute public health threats by causing widespread and difficult to treat infections, such as MRSA (Multidrug-Resistant Staphylococcus aureus). One source of these infections is the use of bacterially contaminated medical devices. Using highly sensitive optical methods, CDRH scientists are developing improved techniques to rapidly detect and identify these bacteria. These new methods, which do not require direct contact with the contaminated surfaces, will allow healthcare personnel to quickly evaluate devices that may be contaminated with harmful bacteria.

TERRORISM MITIGATION

- **Assuring the Safety of X-ray Security Screening Systems**
  CDRH regulates the manufacturers of x-ray systems used for security screening at airports and elsewhere. It is important that such systems meet safety standards to assure that passengers will not be exposed to unnecessary radiation and any associated risks without compromising screening for dangerous materials. To that end, CDRH has provided technical analysis to the Transportation Security Administration (TSA) to address new security system configurations and operating modes, including portals, partial-body systems, and products that use radioactive material as the radiation source, as well as standards for equipment used to screen cargo and vehicles. [94]

MANUFACTURING

- **Rapidly Assessing Medical Device Durability**
  Fatigue, the process by which a material fractures under repeated mechanical loading, is a major concern for medical devices, where fractures can have serious health effects. A newly developed fracture testing method, Fatigue-to-Fracture (FtF) testing, is faster than the current "test to success" method, and it can predict when and how failures may occur. FtF methods are important to implementing medical countermeasures, because FtF could be used to certify new medical device manufacturing processes and facilities faster than current durability testing methods if an attack were to destroy existing manufacturing facilities. CDRH is pilot testing the use of FtF testing for cardiac stents, with the ultimate goal of contributing to the creation of a standard test method. FtF can help reduce pre-clinical testing time and, in the event of a disaster, help industry certify new manufacturing processes and plants to get devices to patients more quickly.

- **Creating Multi-purpose, Non-coring Hypodermic Needles**
  Special hypodermic needles are needed to penetrate the silicone ports that are implanted under the skin of chronically ill patients. These ports allow convenient, long-term access to veins for repeatedly withdrawing blood or administering medications, nutritional products and other liquids. Ordinary needles cannot be used for this purpose because they can "core"—that is, they can cut slivers of silicone from the under-skin port. These silicone slivers can cause leakage around the port and can produce serious health effects if they enter the patient's bloodstream. Huber needles are specially designed to be non-coring. CDRH scientists are investigating whether conventional hypodermic needles can be designed with non-coring properties, thus leading to universal, multi-purpose needles. These might be less expensive than Huber needles and, in the event of a national disaster, would eliminate the concern that Huber needles might be in short supply.

Developing methods to test non-coring hypodermic needles

G.
Improving Health of Pediatric and Other Special Populations

WOMEN'S HEALTH

- **Making Coronary Angioplasty Safer for Women**
  Coronary angioplasty, also known as percutaneous coronary intervention (PCI), is a widely used and effective way to treat coronary artery disease. However, bleeding and vascular complications are a frequent complication of PCI. Women are at higher risk for PCI-related bleeding than men. This risk may be reduced by using the radial artery instead of the traditional approach employing the femoral artery. But transradial PCI may be more challenging in women due to their smaller bodies and narrower arteries. CDRH is collaborating with FDA's Center for Drug Evaluation and Research (CDER) and academic researchers on a project that will evaluate the use of the radial artery in women compared with the femoral artery. This study will help improve the treatment of women with cardiovascular disease.

- **Increasing Women's Representation in Device Trials**
  Women have historically been underrepresented in clinical research, due in part to policies that intentionally excluded women of childbearing age in order to prevent harm to the fetus. Although such policies have been revised, underrepresentation of women persists. This persistent underrepresentation is problematic because gender differences in the nature, diagnosis, and treatment of various diseases can lead to missed diagnoses or fewer referrals to specialists. Collaborating with stakeholders, CDRH has conducted gap analysis to improve enrollment and analyzed postmarket data for signals regarding how devices affect gender differently. This analysis is helping us determine how to achieve appropriate gender representation in device trials and how to conduct scientifically valid analyses for sex differences, given the challenges unique to device trials. [95, 96]

DISABILITIES

- **Making Devices Accessible to Disabled Individuals**
  Individuals with disabilities often do not receive needed medical treatment because certain types of medical devices may not be accessible to them. For example, non-ambulatory patients with multiple sclerosis are 3.2 times less likely to have a mammogram and 5.3 times less likely to get a cervical smear test than their ambulatory counterparts. CDRH is working with the U.S. Access Board and NIH's National Institute on Disability and Rehabilitation Research to identify the technical characteristics that can make a medical device accessible to disabled people. To help do this, we have established a new Human Device Performance Laboratory where we can measure the performance and interactions of medical devices as they might apply to disabled people. CDRH is researching how user characteristics, such as physical capabilities and prior training; environmental conditions, such as light and sound levels; and device features, particularly small but important design differences across device models, can contribute to or reduce medical device use errors and affect patient outcomes. This effort will help identify the technical parameters required to assure that devices are accessible for people with disabilities. It can also result in safer and more accommodating devices for everyone.

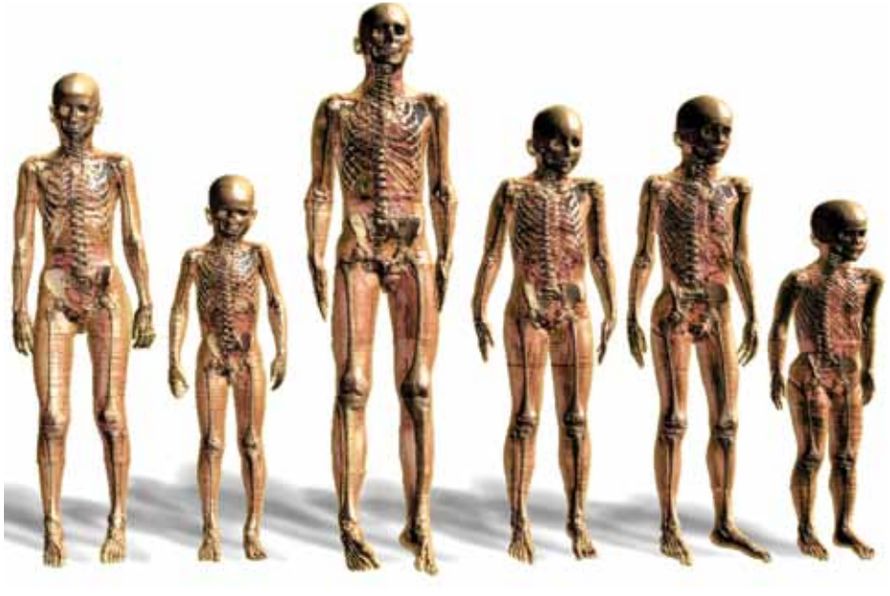
PEDIATRICS

- **Advancing the Treatment of Heart Disease in Children**
  There is an urgent need for safe and effective medical devices to repair congenital and acquired heart defects in children. Congenital heart defects are among the most common of all birth defects and frequently require complex, life-long medical and surgical intervention. Yet this treatment often involves adapting an adult device to meet the child's need because no pediatric devices have been developed for this purpose. CDRH is engaged in projects to accelerate the development of pediatric cardiovascular devices and to evaluate devices currently in use. [97]

  For example, CDRH collaborated with a national clinical society to develop the IMPACT Registry, the first national database to collect performance data on devices implanted to treat congenital heart disease in children and adults. With these data, we can assess prevalence, demographics, patient management, and outcomes. This will allow us to evaluate device performance and help improve cardiovascular care for children. [98]

  Mechanical circulatory support devices help a failing heart to function. These devices may save lives, but they can lead to complications, including infections, thrombosis and device failure. To help determine the nature and magnitude of these problems, CDRH worked with NIH, CMS, and academia to establish INTERMACS, a national tracking registry for patients who are receiving mechanical circulatory support to treat advanced heart failure. INTERMACS is also providing data collection and patient tracking for pediatric ventricular assist devices, which are presently experimental. This will facilitate pre-approval clinical studies of these new and potentially life-saving devices for children. [99]

- **Using Computational Modeling to Improve Defibrillation in Children**
  Because children's cardiac anatomy is so different from adults, they are poorly served by existing defibrillation devices, which have been optimized and studied for use only in adults. Manufacturers have been reluctant to modify existing devices to accommodate children's needs because this is an expensive and high-risk endeavor. Using a Virtual Family of mathematical models that represent both adults and children, CDRH is collaborating with academia to predict the best ways to defibrillate children. By identifying best practices for defibrillator lead placement, shock waveform, and amount of electrical energy that are appropriate for children, this project will help improve the effectiveness of defibrillation in children and save them from cardiac arrest.



Computer generated Virtual Family for evaluating devices

- **Analyzing the Effects of Breast Pumps on Infant Health**
  Pediatricians recommend that infants receive breast milk through the first year of life. About 85% of mothers who breastfeed their infants use a breast pump, but little is known about the benefits and risks of using the pumps. CDRH is working with academia to develop a model that will determine how using a breast pump affects a mother's infant feeding practice and how it may affect the infant's growth and health status after the first year.

- **Evaluating the Neurological Effects of Pediatric Cardiovascular Surgery**
  Complex surgical interventions for pediatric heart disease can result in neurological and cognitive impairments. Monitoring these impairments and their effects on quality of life throughout childhood requires standardized protocols and validated tools and endpoints. CDRH is working with experts from a variety of disciplines to develop these protocols, which should enable us to better evaluate the possible adverse neurological outcomes that can occur after heart surgery on children. [100]

APPENDIX II
Looking to the Future:

New Directions for Regulatory Science in CDRH

See the Index for a full list of projects.

As outlined in this report, CDRH science has helped provide a solid foundation for important regulatory decisions and helped enable medical device innovations. However, newer medical device technologies are emerging that will change the practice of modern medicine and the nature of patient care. These developments are setting a new agenda for our regulatory science efforts in the future. This Section highlights some of the future trends in new technology areas and assessment methods, based on internal CDRH analysis, including horizon scanning, and external reports from government, industry, and academia. It will be essential for us to keep up with these changes and be prepared to regulate the resulting products effectively. This will enable us to facilitate the deployment of important new technologies quickly and cost-effectively. [101]

A. Emerging Technology Trends

- **"Smart" Devices**
  The development of "smart" medical devices is on the rise, in part due to the decreasing cost of electronic components and batteries, a rising trend in miniaturization of components, increasing sophistication of manufacturing technology, the increased use of mobile phones, the availability of tools to evaluate software in smart computerized devices, and ready accessibility of technology to interconnect components that can stream constant data. CDRH will work to ensure that its regulatory science keeps pace with the increasing development and use of smart devices.

- **Medical Robotics**
  The use of robotics in medical applications is another advanced engineering technology that is rapidly growing

in scope and complexity. Systems are in use or under development for an increasing number of surgical applications, augmentation of therapy in rehabilitation settings, replacement of musculoskeletal and cognitive function, and individualized medical care. Further, there are new applications of intelligent machines for diagnostic purposes and for enhanced processing of biological tissues. The development of new robotic systems and applications for use in medicine presents unique challenges for industry and regulatory agencies. CDRH will be developing standards and methods to address the safe design of personal care and medical robots that are designed to collaborate with humans. This work will define specific ways to minimize risks and enhance the safety of these devices.

- **Synthetic Organs and Assistive Devices**
  A broad array of innovative organ replacements and assists are under development in many U.S laboratories. Such prosthetic devices range from the artificial pancreas to "smart" robotic prosthetic limbs. There is increasing research in the newest generations of tissue engineered products, and in neurological devices such as artificial sensory organs and brain-controlled prosthetics. To lay the groundwork for science-based decision making, CDRH will be working on identifying key performance characteristics and criteria, and on validating new measurement methods.

- **Nanotechnology and MEMS products**
  CDRH continues to support the responsible development of medical devices that may contain nanomaterials and other miniaturizing technologies. Current nanotechnology research and development has targeted applications including implant coatings, diagnostic products, and precise delivery of therapeutic agents inside the body. In a parallel technology, research and development is accelerating for micron-scale products based on micro-electro-mechanical systems (MEMS). MEMS devices (often wirelessly linked) are focusing on applications including advanced implantable sensors (e.g., cardiac pressures, biochemical substances, and temperatures) and lab-on-a-chip technologies. For both nanotechnology and MEMS, CDRH scientists will concentrate on issues such as developing new methods to detect any potentially harmful impact of new miniaturized structures on human tissue, and will develop validated methods to evaluate their size, distribution, and performance.

- **Minimally Invasive Devices**
  Devices that support minimally invasive medicine are being developed along several lines. Minimally invasive implants include flexible ophthalmic implants and cardiovascular products that do not require open chest surgery. Transdermal surgical techniques are advancing through the use of various types of radiation, including ultrasound and ionizing radiation. Non-invasive diagnostic techniques also include optical diagnostic technologies employing light to detect disease under the skin and in body cavities. As these products are being developed, CDRH scientists will be clarifying the underlying processes that determine safety and effectiveness, and developing reliable test methods for use by industry and FDA.

- **Imaging**
  Significant advances in imaging systems will improve non-invasive diagnostic capabilities. These include dynamic contrast-enhanced magnetic resonance imaging, multi-modality imaging, image fusion, breast tomosynthesis, dedicated breast computed tomography, and image-guided surgical systems, all under development by academia and industry, with a broad range of performance characteristics.

These systems promise vastly improved diagnostic imaging capabilities. Fulfilling this promise will require a detailed understanding of the algorithms and physics employed by these systems, and the development and validation of reliable methods for characterizing their safety and effectiveness. By targeting these issues, CDRH scientists will facilitate the availability of new imaging systems and assure that they are safe and effective.

- **Rapid Screening Devices**
  During times of national emergency or disaster, there will be a need to quickly and precisely identify biothreat agents and assess candidates for vaccines. These activities will be needed in locations that are decentralized or even remote. CDRH has ongoing and proposed research in several related areas, including infrared fiber-optic methods for remote sensing of bacterial pathogen contamination; inexpensive, battery-powered devices to provide diagnostics outside traditional laboratory settings ("lab-on-a-chip"); and flow cytometry to evaluate cellular responses to pandemic flu, viral and bacterial bioterror agents.

  New diagnostic devices are being designed to simultaneously differentiate between a large number of biological threat agents by identifying and genotyping various pathogens. Establishing and validating the performance of these multiplex devices, which are used to make important clinical and public health decisions, is scientifically challenging. CDRH will develop and qualify methods to expedite the regulatory process for these innovative devices, facilitating their availability in the event of a crisis.

- **Medical Devices for Home- and Self-Care**
  More and more medical devices will be used by patients and their lay caregivers at home. Many of these will be the sorts of "smart" wirelessly-networked noted above. Many will also be wearable products with miniaturized components. In addition to the technology issues that accompany such designs, home- and self-care products present important human-factors considerations. Patients may need to learn how to use a device at the same time they are learning how to manage a new health condition with its associated effects on their physical abilities and emotional state. The labeling, packaging, instructions, training, and other reference materials that accompany the device are vital to its safe use under these circumstances. CDRH will employ social sciences approaches to ensure that these materials will anticipate the needs of all users of the device, and that they will be provided in a variety of formats considering age, physical and cognitive abilities, and knowledge and experience levels, as well as the overall literacy and health literacy of users.

B.
Emerging Assessment Tools

- **Computational Modeling**
  The use of computer modeling has the potential to streamline the design, assessment and evaluation of medical devices. These models could also make clinical trials more efficient by focusing on the most critical parameters in determining safety and effectiveness. CDRH will develop a framework for validating computer models for regulatory assessment, and will facilitate the development of computer models that are based on population characteristics and closed-loop systems.

- **Next Generation of Personalized Medicine — The Virtual Physiological Patient**
  Computer modeling and simulation will be essential in creating truly personalized medicine. Personalized medicine requires more than a personalized genome, it requires personalized functional anatomy. Although developing computer models of healthy human physiology is of fundamental importance, designing interoperable computer models and simulations of diseased human states is needed as well and within reach. CDRH will continue efforts to move personalized medicine forward. This will include the development of a Library of Models to house publically available, FDA validated computer models of the human body in different disease states. We plan to make this Virtual Physiological Patient accessible to researchers and medical device developers for testing new device designs and applying for device clearance and approval.

- **Wireless Device Systems**
  With the burgeoning use of wireless products that emit electromagnetic radiation, there is increasing concern about electromagnetic interference with medical devices, and about the reliability of data that is transmitted data wirelessly through connected device networks. These are important issues in hospital settings, where conditions of use can vary widely between a private patient room, intensive care unit, operating suite, or emergency department. They are especially significant where a high number of medical and non-medical devices (such as cell phones) may be simultaneously in use. Special situations such as emergency transport and mass casualty events pose additional challenges. CDRH engineers will expand our research efforts to mitigate these problems.

- **Interoperability of Computerized Medical Devices**
  Medical device or medical system interoperability usually implies that systems can exchange data with each other and control each other's functions. Although these integrated systems can provide a safety buffer in preventing medical errors, it is possible for them to pose safety problems of their own. CDRH will work to improve interoperability among diagnostic and therapeutic medical devices and ensure that interoperability does not pose a hazard to patients.

- **Genomics**
  Technologies for accessing a patient's full genomic sequence are now under intensive development, along with new genomic tests for disease detection, prevention and personalized therapies. This will necessitate the development and validation of reliable tools to characterize these products and assure that they are accurate and appropriate. CDRH will play a significant role in this effort, helping to open the way for major advances in patient care.

- **Biomarkers**
  Biomarkers play an important role in public health. Biomarker development is needed to: detect damage to organs; develop approaches to predict the toxicity of compounds released from devices; evaluate the interactive effects of compounds released from devices; and characterize the exposure of patients to compounds released from medical devices. As CDRH continues to qualify the use of biomarkers in clinical settings, we will also strive to develop new biomarkers to aid in determining the safety and effectiveness of medical devices.

- **Sterilization and Infection Control**
  Practical, mobile methods are needed for detecting, monitoring, and managing the spread of infection in healthcare environments and among the general public during an emergency. CDRH will continue to study decontamination of devices such as personal protective equipment that are not intended to be reused under normal circumstances but may need to be reused in a crisis. Surgical facemasks and respirators will also undergo testing to judge their effectiveness against aerosols.

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