

Subcommittee to the FDA Science Board

The Commissioner's Charge Statement to the Science Board

Review and report the broad categories of scientific and technologic capacities that FDA needs to fully support its core regulatory functions and decision-making throughout the product life cycle, today and over the next decade. Specifically:

- Are there any important gaps in current scientific capacities in which FDA should substantially increase efforts to ensure that it can address current or expected scientific demands of FDA's regulatory mission? In what areas should the Agency maintain or strengthen its current level of work and capacity?
- Are there areas of science in which the Agency should consider refocusing its efforts in order to better address current or anticipated future scientific demands of FDA's regulatory mission?
- What opportunities exist to enhance the overall effectiveness of FDA's scientific and technologic capacity through coordination of scientific activities and priority-setting across FDA components?
- What opportunities exist to better leverage FDA's scientific capacity through collaboration with other public agencies and private organizations? Are there other approaches to resource leveraging that FDA could pursue to better support needed scientific capacities?

Background and Rationale for Current Review

Although this is not the first review of the FDA, the Committee views the timing of this review as critical in charting FDA's future course. It comes in the year of the 100th anniversary of the Agency, a time of unprecedented scientific opportunities to allow reduction of uncertainty in the regulatory process; a time of increasingly complex product reviews based on scientific advances and globalization; a time of increased scrutiny of the Agency by its stakeholders; and a time of declining budgets in real dollars. This environment presents both a challenge and an opportunity for FDA to pursue a deliberative process that will focus on ensuring the continued quality and productivity of the Agency's science base. Never before have there been such opportunities to leverage the expertise and resource needs with external partners as outlined in the FDA's Critical Path Initiative. The presence of a new Commissioner with unique experience in clinical research in both academia and government strengthens this opportunity, as does the implementation of NIH's Road Map Initiative

with emphasis on translational research and CDC's new emphasis on prevention research.

Historical Perspective of FDA Reviews

A number of reviews by previous Science Board and other external committees have examined aspects of FDA's science programs. For example, several reports have unanimously and emphatically affirmed that the presence in the FDA of a vigorous, high-quality intramural program of scientific research provides the essential foundation of sound regulatory policy and performance, and ensures that the FDA is and will continue to be best positioned to carry out its statutory responsibilities. However, this is not necessarily appreciated by the public, policymakers and other stakeholders, including industry.

The FDA needs to communicate, both internally and externally, a clear vision of the fundamental role of science in the regulatory process. This vision should define the role of science in developing relevant guidance documents and in developing, modifying and approving appropriate standards. The vision should delineate the role of science in determining how effectively FDA responds to new technologies and facilitates the introduction of those technologies to consumers in a safe and effective manner. Development of a system for summarizing the scientific and other factors leading to guidances or approvals (or rejections) would be useful for FDA, as it reviews its decisions, as well as for the public. Therefore, it is important that the current review enumerates examples that illustrate the diversity and quality of FDA intramural science accomplishments that have had major impacts on the regulatory mission of the Agency.

Goals of the Present FDA Review

The major goal of this review will be to determine how science is currently being used to address FDA's evolving regulatory challenges, with specific objectives: to identify where enhanced internal scientific expertise will be needed to maintain the Agency's high standards of regulatory decision making in the face of rapidly changing technology; to determine if FDA is doing what is needed to evolve FDA's professional expertise so as to be able to review new kind of products in a knowledgeable way; to evaluate if scientific expertise is being effectively used; to determine if regulatory science and research projects achieve relevant regulatory goals and if those goals are still relevant; and finally, to identify the biggest future challenges facing each of the Centers as well as the major barriers to addressing them.

The Committee will assess the many facets of how the Agency invests in and maintains its intellectual capital. The review will focus on FDA-wide scientific peer review; recruitment and retention of outstanding scientific personnel; invigorating training programs that transcend Center and program lines; instituting efficient management and review

practices that ensure the science enterprise is responsive to evolving regulatory needs; and exploring opportunities for increased collaboration with the extramural community, including industrial and academic and other governmental laboratories. The goal will be to make recommendations to create more uniform and consistent processes for setting priorities and ensuring quality across the FDA. The Committee will identify defining principles which will guide the direction of resources to the highest priority activities.

Given the breadth of subjects and time frame, it is not feasible for the Review committee, to visit individual Centers and laboratories, or to conduct specific evaluations of individual scientists, laboratories or programs. Rather, the Committee will undertake a high-level review of the state of the science in the FDA and focus its attention on the organization of the scientific programs, their interactions with the extramural scientific community, and the policies, procedures and standards that govern their conduct. Three areas that are perceived to be common to all Centers and which need immediate attention will be examined in detail. These include: genomics, information technology infrastructure, and post-marketing surveillance processes.

The Review Process

The Review will take place in two phases. Phase I will be a trans-FDA program fact-finding effort by an internal committee. The fact-finding effort will focus on identifying general characteristics of the science effort as well as special features of the various Centers and programs that make up FDA. This includes distinguishing the common and unique features of science programs across FDA; their complementarities to the FDA regulatory mission; the impact of decision-making processes and other factors that shape the role, size, and scientific staff (composition, recruitment, and retention); the nature and process of research evaluation; and issues in review. Another major element of the internal fact-finding will involve the science infrastructure with special consideration of the new White Oak facility, which offers opportunities for consolidation and promotion of synergy across programs. Since important differences exist across the intramural programs of the individual Centers and programs — a reflection of their distinctive missions — data explaining the variations among the Centers will also be gathered. The fact-finding committee will be guided by an executive working group and four Subcommittees including IT infrastructure, genomics, post-marketing surveillance, and general infrastructure issues. A broad range of Center directors, other key administrators and senior intramural research and review scientists should be represented in the working group.

Specifically, the internal review will gather data on: Human and Physical Resources; Intellectual Environment; Administration of Science; How is the Scientific Staff Chosen; Quality Control: The Individual Peer Review Process; The Training Function and Career

Development; Scientific Interactions with Industry, Academia, other Government Scientists; the White Oak Facility; Measures of Productivity and Impact of the FDA Intramural Research Program on the regulatory mission; Budgetary Resources over the past 10 years (budget formulation and execution processes, and each Center's and Office of Regulatory Affairs best estimates of absolute and relative expenditure of resources on research and laboratory testing, including budget and personnel); and Mechanisms for inter- and intra-Center communication to improve the scientific support infrastructure and collaborations within FDA and with the external scientific community with special emphasis upon intramural NIH and CDC scientists.

Phase II of the review will be carried out by a group of external advisors composed of four members of the Science Board and additional representatives from industry, academia, and other federal agencies. The data from Phase I will be reviewed plus interviews will be conducted by the external committee with the following: Secretary HHS; the NIH Director as well as selected NIH institute Directors; FDA leaders, center directors, and senior scientists, and other stakeholders, including research executives from industry (biotech, large pharma, and device companies via the respective trade organizations). The Subcommittee will be divided into nine groups based on expertise, and will then be assigned to the review of one of the following: Centers for Drug Evaluation and Research, Biologic Evaluation and Research, Food Safety and Applied Nutrition, Toxicology Research, Veterinary Medicine, Devices and Radiologic Health, Genomics, Information Technology, and Surveillance and Statistics.

Draft Report Template Developed by the Subcommittee to Guide the Review

Section I – Defining Major Goal

This section would define the overarching goals of the Agency and define the critical needs in a regulatory context (e.g., reducing uncertainty in regulatory decision making).

Section II – Identifying Current and Future Scientific Regulatory Challenges and How They Are Being Addressed

The purpose of this section would be to detail the perceived current and future regulatory challenges. The identification of these challenges would be by both FDA components and FDA stakeholders, so that several points of view are captured. Since the ability of FDA to identify the key scientific regulatory challenges and propose solutions is critical for the Agency to effectively manage its scientific resources, it is important to review the processes by which FDA identifies and addresses these challenges. (For example, many of the principles contained in the Critical Path white paper may now seem self-evident; what process did the Agency use to identify and articulate these?; and would they apply to areas other than medical product development?)

Data: Two types of information could be collected for this section:

- Perceived current and future challenges. Input would come from FDA and FDA stakeholders and might include such areas as:
 - Increasing numbers of applications
 - New types and increased volume of data
 - New types of products
 - Globalization
 - Areas of scientific uncertainty in regulatory requirements and decision making
- Information on FDA processes for identifying and addressing current and future scientific regulatory challenges.
- Current Portfolio of FDA Science Programs (table)

Section III – Identification of Science Gaps

Purpose of this section would be to ask for input on more specific identified scientific gaps and needs required to meeting the scientific challenges articulated in Section II. These gaps would be from assessments from FDA and FDA stakeholders (e.g., what major scientific gaps need to be filled from FDA and stakeholder perspective). This could be reported in generalized areas but not listing specific projects (e.g., similar to the Critical Path report's identification of 6 major topics, without getting to the detail of the Critical Path opportunities list).

Emphasis could be placed on those broad areas which span several FDA Centers (e.g., genomics, post-market surveillance, methods of receiving, storing and mining large datasets, refining statistical and trial design issues).

Section IV – Trends Affecting FDA's Regulatory Responsibilities and Resources

This Section would contain a factual compilation of quantitative temporal trends in a number of areas that impact the ability of Agency to address the future challenges and hurdles detailed in sections II & III, and would also identify radical changes that are occurring in the regulatory demographics and increased responsibilities in the FDA regulatory inventory. Trends could be in a number of areas and might include:

Science investment:

- NIH
- CDC
- Industry R&D – US
- Industry R&D developed by the Subcommittee to guide the review – foreign
- FDA total appropriated
- FDA science programs

Staffing:

- NIH
- CDC
- Industry R&D – US
- Industry R&D – foreign
- FDA (breakdown of scientists by category and expertise)

Regulated products and businesses (could be center specific):

- Number of new regulated product categories
- Number of regulated products
- Number of regulated firms

Number of FDA submissions utilizing novel technology or data:

- Combination products
- Nanotechnology products
- Therapeutic proteins
- Recombinant or transgenic products
- Pharmacogenomic submissions

External scientific partnerships and collaborations:

- CRADAs
- Memorandum of Understanding
- InterAgency Agreements
- Others

Other trend categories.

Section V – Recommendations

This section could include all recommendations resulting from the Science Board Review and discussions. Recommendations could fall into several categories:

1. Recommendations regarding the process FDA uses to periodically evaluate regulatory scientific challenges and to prioritize its science portfolio
2. Recommendations regarding the balance of FDA's current portfolio (e.g., what areas need additional attention, which areas need less?)
3. How can FDA better leverage collaborations and other avenues (e.g., establishment of an FDA foundation) to help address these critical areas. This would include discussion of how to better integrate across the Agency efforts in broad, cross-cutting areas that are common to several centers (e.g., genomics, post-market surveillance, methods of receiving and handling large datasets, refining statistical and trial design issues).

Section VI – Conclusions

This section could include the committee's overall impression of FDA science programs. If there are more global recommendations, beyond what the Agency can implement alone, this section would be an appropriate place to include them.

Roster of Subcommittee Members and Advisors to the Subcommittee

Science Board Subcommittee Members	
<p>Gail H. Cassell, MS, PhD, DSc (Hon); Subcommittee Chair Vice President, Scientific Affairs and Distinguished Lilly Research Scholar for Infectious Diseases Eli Lilly and Company</p>	<p>Barbara J. McNeil, MD Ridley Watts Professor and Head Department of Health Care Policy Professor of Radiology Harvard Medical School</p>
<p>Allen D. Roses, MD, FRCP (Hon) Jefferson-Pilot Professor of Neurobiology and Genetics Professor of Medicine (Neurology) Director, Deane Drug Discovery Institute Senior Scholar, Fuqua School of Business Senior Vice President, Pharmacogenetics GlaxoSmithKline (retired 9/07)</p>	
External Advisors to the Subcommittee	
<p>David Altshuler, MD, PhD Founding Member and Director, Program in Medical and Population Genetics, Broad Institute of Harvard and MIT Associate Professor of Genetics and Medicine Harvard Medical School and Massachusetts General Hospital</p>	<p>Barbara Alving, MD Director National Center for Research Resources National Institutes of Health</p>
<p>Leslie Z. Benet, PhD (Subgroup Chair: Center for Biologics Evaluation and Research) Professor, Department of Biopharmaceutical Sciences University of California, San Francisco</p>	<p>D. Bruce Burlington, MD Executive Vice President for Business Practices and Compliance Wyeth Pharmaceuticals (retired 7/07)</p>
<p>Robert Califf, MD Director of the Duke Clinical Research Unit Professor of Medicine, Division of Cardiology Duke University Medical Center</p>	<p>C. Thomas Caskey, MD Chief Operating Officer and CEO-/Director-Elect The Brown Foundation Institute of Molecular Medicine Executive Vice President of Molecular Medicine & Genetics University of Texas Health Science Center at Houston</p>
<p>P. Joan Chesney, MD Director, Office of Academic Programs and Member, Department of Infectious Diseases St. Jude Children's Research Hospital Professor of Pediatrics, Division of Infectious Diseases and Associate Dean for St. Jude Academic Affairs University of Tennessee College of Medicine Former Chair FDA Pediatrics Advisory Committee and Member, FDA Anti-infectives Drug Advisory Committee</p>	<p>David L. DeMets, PhD Professor and Chairman Department of Biostatistics & Medical Informatics University of Wisconsin</p>

External Advisors to the Subcommittee	
<p>Susan Desmond-Hellmann, MD, MPH (Subgroup Chair: Center for Drug Evaluation and Research) President, Product Development Genentech, Inc. Former member HHS Advisory Committee on Regulatory Reform</p>	<p>Susan Ellenberg, PhD (Subgroup Chair: Surveillance, Statistics) Professor of Biostatistics Associate Dean for Clinical Research University of Pennsylvania School of Medicine Center for Clinical Epidemiology and Biostatistics</p>
<p>Garret A. FitzGerald, MD Professor of Medicine and Professor and Chair of Pharmacology Department of Pharmacology University of Pennsylvania School of Medicine</p>	<p>Alfred Gilman, MD, PhD Nobel Laureate Physiology and Medicine Dean, Southwestern Medical School and Regental Professor, Department of Pharmacology University of Texas Southwestern Medical Center at Dallas</p>
<p>Robert Goldstein, MD, PhD (Subgroup Chair: Genomics) Chief Scientific Officer Juvenile Diabetes Research Foundation International</p>	<p>Leroy E. Hood, MD, PhD President Institute for Systems Biology</p>
<p>Peter Barton Hutt Senior Counsel Covington & Burling LLP Former Chief Counsel FDA</p>	<p>Evan Kharasch, MD, PhD Russell D. and Mary B. Sheldon Professor of Anesthesiology and Director, Division of Clinical and Translational Research Washington University School of Medicine</p>
<p>Sangtae Kim, PhD (Subgroup Chair: Information Technology) Donald W. Feddersen Distinguished Professor Purdue University Former VP Information Technology Eli Lilly and Pharmacia</p>	<p>Julia Lane, PhD Senior Vice President Director, Economics, Labor and Population NORC/University of Chicago</p>
<p>Cato T. Laurencin, MD, PhD Lillian T. Pratt Distinguished Professor of Orthopedic Professor of Biomedical and Chemical Engineering University of Virginia</p>	<p>Jeffrey M. Leiden, MD, PhD Partner, Clarus Ventures, LLC President & Chief Operating Officer Pharmaceutical Products Group Abbott Laboratories (retired)</p>
<p>J. Glenn Morris, MD, MPH, TM Director Emerging Pathogens Institute University of Florida, Gainesville</p>	<p>Philip Needleman, PhD, MS, BS Chief Scientific Officer, and Senior Executive Vice President Pharmacia (retired)</p>
<p>Robert M. Nerem, PhD (Subgroup Chair: Center for Devices and Radiological Health) Parker H. Petit Professor and Director Institute for Bioengineering and Bioscience Georgia Institute of Technology</p>	<p>Dale Nordenberg, MD Managing Director, Healthcare Industry Advisory PriceWaterhouseCoopers Former Associate Director for Informatics and Chief Information Officer National Center for Infectious Diseases Centers for Disease Control and Prevention</p>
<p>J. Marc Overhage, MD, PhD Informatics and Electronic Medical Records Research Scientist, Regenstrief Institute, Inc. Associate Professor of Medicine Indiana University School of Medicine</p>	<p>Jim E. Riviere, DVM, PhD (Subgroup Chair: Center for Veterinary Medicine) Burroughs Wellcome Fund Distinguished Professor and Director Center for Chemical Toxicology Research and Pharmacokinetics, and Biomathematics Program</p>

External Advisors to the Subcommittee	
<p>Eve Slater, MD, FACC Senior Vice President–Worldwide Policy Pfizer Inc. Former Asst. Secretary for Health and Human Services Former Vice President – Global Regulatory Affairs Merck Medicines and Vaccines</p>	<p>John A. Thomas, PhD (Subgroup Chair: National Center for Toxicological Research) Adjunct Professor Indiana School of Medicine</p>
<p>P. Roy Vagelos, MD Retired Chairman and CEO of Merck & Co., Inc.</p>	<p>Catherine E. Woteki, PhD (Subgroup Chair: Center for Food Safety and Applied Nutrition) Global Director of Scientific Affairs Mars, Inc. Former Undersecretary for Food Safety in the US Department of Agriculture and Dean, Iowa State University College of Agriculture</p>

Biographical Profiles of Subcommittee Members and Advisors to the Subcommittee

Gail H. Cassell, MS, PhD, DSc (hon) – Subcommittee Chair

is currently Vice President, Scientific Affairs and Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly and Company in Indianapolis, Indiana. She is the former Charles H. McCauley Professor and Chairman of the Department of Microbiology at the University of Alabama Schools of Medicine and Dentistry at Birmingham, a department which ranked first in research funding from the National Institutes of Health during the decade of her leadership. She obtained her BS from the University of Alabama in Tuscaloosa and in 1993 was selected as one of the top 31 female graduates of the 20th century. She obtained her PhD in Microbiology from the University of Alabama at Birmingham and was selected as its 2003 Distinguished Alumnus.

She is a past President of the American Society for Microbiology (the oldest and single largest life sciences organization with a membership of over 42,000). She was a member of the National Institutes of Health Director’s Advisory Committee and a member of the Advisory Council of the National Institute of Allergy and Infectious Diseases of NIH. She was named to the original Board of Scientific Councilors of the Center for Infectious Diseases, Centers for Disease Control and served as Chair of the Board. She recently served a three-year term on the Advisory Board of the Director of the Centers for Disease Control and as a member of the Secretary of Health and Human Services Advisory Council of Public Health Preparedness. Currently she is a member of the Science Board of the Federal Food and Drug Administration. Since 1996 she has been a member of the US–Japan Cooperative Medical Science Program responsible for advising the respective governments on joint research agendas, (US State Department/Japan Ministry of Foreign Affairs). She has served on several editorial boards of scientific

journals and has authored over 250 articles and book chapters. Dr. Cassell has received national and international awards and an honorary degree for her research in infectious diseases. She is a member of the Institute of Medicine (IOM) of the National Academy of Sciences and is currently serving a three-year term on the IOM Council, the governing board.

Dr. Cassell has been intimately involved in establishment of science policy and legislation related to biomedical research and public health. For nine years she was chairman of the Public and Scientific Affairs Board of the American Society for Microbiology; has served as an advisor on infectious diseases and indirect costs of research to the White House Office of Science and Technology Policy, and has been an invited participant in numerous Congressional hearings and briefings related to infectious diseases, anti-microbial resistance, and biomedical research. She has served two terms on the LCME, the accrediting body for US medical schools as well as other national committees involved in establishing policies in training in the biomedical sciences. She has just completed a term on the Leadership Council of the School of Public Health of Harvard University, and years of service on the Executive Committee of the Board of Research!America. Currently, she is a member of the following organizations: Executive Committee of the Board of Visitors of Columbia University School of Medicine, Board of Directors of the Burroughs Wellcome Fund, and Advisory Council of the School of Nursing of Johns Hopkins.

Barbara J. McNeil, MD – Subcommittee Member is the Ridley Watts Professor and founding Head of the Department of Health Care Policy at Harvard Medical School. She is also a Professor of Radiology at Harvard Medical School (HMS) and at Brigham and Women’s Hospital (BWH). She has worked in the fields of health policy and radiology (nuclear medicine) for over 25 years at Harvard Medical School and the Brigham and Women’s Hospital. She has had extensive experience in clinical care and health policy research.

Dr. McNeil is considered a leader in the evaluation of diagnostic technologies, in the utilization of evidence based medicine for patient care decisions, and in the coverage process for new technologies (drugs, devices, and procedures). Because of these experiences and her ongoing research and clinical work she has a broad view of the health care delivery system. She has had broad experiences in advising at the federal level and for multiple private (publicly held, for-profit, and not-for-profit) organizations in health care.

Dr. McNeil’s research activities have focused on several areas, most notably technology assessment and quality of care. Her most recent work includes two large studies supported by the Department of Veterans Affairs in the United States. The first focused on a comparison of quality of care for veterans with cardiac disease and the

second for those with cancer. Dr. McNeil also works closely with the national Blue Cross Blue Shield Association in several areas related to the identification and dissemination of approaches to improving either the quality or the efficiency of care in plans across the country.

Dr. McNeil received her AB degree from Emmanuel College, her PHD from Harvard Medical School, and her PhD from Harvard University. She is a member of the Institute of Medicine (IOM), the National Academy of Sciences, and the American Academy of Arts and Sciences. Dr. McNeil is also a member of the Blue Cross Technology Evaluation Commission (TEC), the Medicare Coverage Advisory Committee, and the Council for Performance Measurement for the JCAHO. She recently began serving as Chair of an IOM committee on the identification of high clinical value services. Previously Dr. McNeil served as a member of the Prospective Payment Assessment Commission and the Publications Committee of the New England Journal of Medicine.

Allen D. Roses, MD, FRCP (Hon) – Subcommittee Member

was appointed as Senior VP, Pharmacogenetics for GlaxoSmithKline, July 2006. Previously, he held the position of Senior VP, Genetics Research for GlaxoSmithKline. In 1997, Dr. Roses joined Glaxo Wellcome and was charged with organizing genetic strategies for susceptibility gene discovery, pharmacogenetics strategy and implementation, and integration of genetics into medicine discovery and development. In the GSK R&D structure, genetics, genomics, proteomics and bioinformatics are part of Genetics Research and support the entire R&D pipeline. His group recently published the proof of principle experiments for using linkage disequilibrium mapping to identify susceptibility loci for drug adverse events. In 1997 when he left Duke University Medical Center, Dr. Roses was the Jefferson Pilot Professor of Neurobiology and Neurology, Director of the Joseph and Kathleen Bryan Alzheimer's Disease Research Center, Chief of the Division of Neurology, and Director of the Center for Human Genetics. Dr. Roses was one of the first clinical neurologists to apply molecular genetic strategies to neurological diseases. His laboratory at Duke reported the chromosomal location for more than 15 diseases, including several muscular dystrophies and Lou Gehrig's disease. He led the team that identified APOE as a major, widely confirmed susceptibility gene in common late-onset Alzheimer's disease. Translation of these findings to pathway analyses, drug discovery and development has continued in GSK.

David Altshuler, MD, PhD is Associate Professor of Genetics and of Medicine, at the Harvard Medical School and Massachusetts General Hospital, and Director, Program in Medical and Population Genetics, at the Broad Institute of Harvard and MIT.

Dr. Altshuler is a human geneticist and clinical endocrinologist whose laboratory aims to characterize and catalogue patterns of human genetic variation, and by applying this information better understand the inherited contribution to common diseases. Dr. Altshuler was a leader in the SNP Consortium and International HapMap Consortium, public-private partnerships that created genome-wide maps of human genetic diversity that now guide the design and interpretation of genetic association studies. His research has contributed to identifying the role of common genetic variants in type 2 diabetes, prostate cancer, age related macular degeneration, and systemic lupus erythematosus.

Dr. Altshuler is a Distinguished Clinical Scientist of the Doris Duke Charitable Foundation, a Clinical Scholar in Translational Research of the Burroughs Wellcome Fund, and is funded by the Richard and Susan Smith Pinnacle Award of the American Diabetes Association and the "Freedom to Discover" Award from the Foundation of Bristol-Myers Squibb. He is past recipient of the Stephen Krane Award of the Massachusetts General Hospital, and the Charles E. Culpeper Medical Scholarship. He is a member of the American Society of Clinical Investigation, and on advisory boards at the National Institutes of Health, Doris Duke Charitable Foundation, and The Wellcome Trust, as well as on the editorial board of Annual Reviews of Human Genetics and Genomics, Current Opinion in Genetics and Development, and the Board of Reviewing Editors at Science Magazine.

A graduate of MIT and Harvard Medical School, Dr. Altshuler received his clinical training in Internal Medicine and Endocrinology at Massachusetts General Hospital. In 2003 he was named one of four Founding Members, and Director of the Program in Medical and Population Genetics, of the Broad Institute of Harvard and MIT, a research collaboration of Harvard, MIT, The Whitehead Institute, and the Harvard Hospitals created to bring the fruits of genomic science to medicine.

Barbara Alving, MD, MACP is the Acting Director of the National Center for Research Resources (NCRR) which funds the development of new technologies for basic and clinical research, supports training for researchers in the biomedical sciences, develops preclinical models, supports clinical research programs, and provides health and biomedical education for the public.

Dr. Alving received her MD cum laude from Georgetown University School of Medicine in Washington, DC After an internship in internal medicine at Georgetown University Hospital, she completed a residency in internal medicine and a fellowship in hematology at the Johns Hopkins University Hospital in Baltimore, Maryland. Dr. Alving then became a research investigator in the Division of Blood and Blood Products at the Food and Drug Administration on the NIH campus. In 1980, she joined the Department of Hematology at the Walter Reed Army Institute of Research and became Chief of the Department in 1992. She left the Army at the rank of Colonel in 1996 to become the Director of the Medical Oncology/Hematology Section at the Washington Hospital Center in Washington, DC. In 1999, she joined the National Heart, Lung, and Blood Institute (NHLBI), serving as the Director of the extramural Division of Blood Diseases and Resources until becoming the Deputy Director of the Institute in September 2001. From September 2003 until February 1, 2005, she served as the Acting Director of the NHLBI. In March 2005 she became the Acting Director, NCRR. From October 2002 until January 06, she served as the Director of the Women's Health Initiative, which is funded through the NHLBI.

Dr. Alving is a Professor of Medicine at the Uniformed Services University of the Health Sciences in Bethesda, a Master in the American College of Physicians, a former member of the Subcommittee on Hematology of the American Board of Internal Medicine, and a previous member of the FDA Blood Products Advisory Committee. She is a co-inventor on two patents, has edited three books, and has published more than 100 papers in the area of thrombosis and hemostasis.

Leslie Z. Benet, PhD, Professor and former Chairman (1978–1998), Department of Biopharmaceutical Sciences, University of California, San Francisco, and Chairman of the Board, AvMax, Inc., received his AB (English), BS (Pharmacy), MS from the University of Michigan and PhD from the University of California. He has received six honorary doctorates: Uppsala University, Sweden (PharmD, 1987), Leiden University, The Netherlands (PhD, 1995), University of Illinois at Chicago (DSc, 1997), Philadelphia College of Pharmacy and Science (DSc, 1997), Long Island University (DSc, 1999) and University of Athens (PhD 2005). His research interests, more than 470 publications, and 11 patents are in the areas of pharmacokinetics,

biopharmaceutics, drug delivery and pharmacodynamics. He is listed among the 250 most cited pharmacologists world-wide. In 1985, he served as President of the Academy of Pharmaceutical Sciences. During 1986, Dr. Benet was a Founder and first President of the American Association of Pharmaceutical Scientists (AAPS). In 1987, Dr. Benet was elected to membership in the Institute of Medicine (IOM) of the National Academy of Sciences. He has received the highest scientific award of AAPS (1989 and 2000), Rho Chi (1990), American Association of Colleges of Pharmacy (1991), American Society for Clinical Pharmacology and Therapeutics (1995), American Pharmaceutical Association (2000), International Pharmaceutical Federation (2001 and the Controlled Release Society (2004). Dr. Benet formerly served as Chair of the FDA Center for Biologics Peer Review Committee and the FDA Expert Panel on Individual Bioequivalence and as a member of the FDA Science Board and the Generic Drugs Advisory Committee. He presently serves as a member of the IOM Forum on Drug Discovery, Development and Translation.

D. Bruce Burlington, MD is an independent consultant on regulatory affairs. As of Sept 2007 he retired from his position as Executive Vice President for Business Practices and Compliance at Wyeth Pharmaceuticals located in Collegeville, Pennsylvania. He is active in PhRMA and public policy development (PDUFA, Biosimilars, and drug safety legislation) including as a subcommittee member of the FDA science advisory committee's review of the state of science at FDA. In his previous appointment at Wyeth, until 2006, he was responsible for the Regulatory Affairs, Safety Surveillance, Quality Operations, Compliance Operations, and Audit Departments.

Graduated with an PHD from Louisiana State University School of Medicine at New Orleans in 1976; Bruce received clinical training at the University of Colorado, and is board certified in Internal Medicine and Infectious Diseases.

In March 1999 Bruce closed his career at the United States Food and Drug Administration where he began as a research fellow, became Chief of the Influenza Vaccines (Respiratory Viruses) Lab, and then headed the Investigational New Drug Division in the Center for Biologics. He moved to the Center for Drug's New Drug Evaluation program in 1988 as Deputy Director of ODE II, and following a year as Director of the Office of Generic Drugs, was acting Deputy Center Director for Medical Affairs from 1991 through 1993. Between 1993 and 1999 he was the Center Director for FDA's Center for Medical Devices and Radiological Health, which oversees the US's regulatory programs for medical devices, in vitro diagnostic products, radiological health, and mammography quality.

Robert M. Califf, MD was born in Anderson, South Carolina, in 1951 and attended high school in Columbia, SC, where he was a member of the 1969 AAAA South Carolina Championship basketball team.

He graduated from Duke University, summa cum laude and Phi Beta Kappa, in 1973 and from Duke University Medical School in 1978, where he was selected for Alpha Omega Alpha. He performed his internship and residency at the University of California at San Francisco and his fellowship in cardiology at Duke University. He is board-certified in internal medicine (1984) and cardiology (1986) and is a fellow of the American College of Cardiology (1988).

He is currently Vice Chancellor for Clinical Research, Director of the Duke Translational Medicine Institute (DTMI), and Professor of Medicine in the Division of Cardiology at the Duke University Medical Center in Durham, North Carolina. For 10 years he was Director of the Duke Clinical Research Institute, the largest academic research organization in the world. He is the editor-in-chief of Elsevier's *American Heart Journal*, the oldest cardiovascular specialty journal. He has been an author or coauthor of more than 650 peer-reviewed journal articles and is a contributing editor for www.theheart.org, an online information resource for academic and practicing cardiologists.

Dr. Califf led the DCRI for many of the best-known clinical trials in cardiovascular disease. With an annual budget of over \$100 million, the DCRI has more than 800 employees and collaborates extensively with government agencies, the medical-products industry, and academic partners around the globe. In cooperation with his colleagues from the Duke Databank for Cardiovascular Disease, Dr. Califf has written extensively about the clinical and economic outcomes of chronic heart disease. He is considered an international leader in the fields of health outcomes, quality of care, and medical economics.

Dr. Califf has served on the Cardiorenal Advisory Panel of the US Food and Drug Administration (FDA) and the Pharmaceutical Roundtable of the Institute of Medicine (IOM). He served on the IOM committees that recommended Medicare coverage of clinical trials and banned Ephedra, and he is currently serving on the IOM's Committee on Identifying and Preventing Medication Errors as well as its Forum in Drug Discovery, Development, and Translation. He is the director of the coordinating center for the Centers for Education & Research on Therapeutics™ (CERTs), a public/private partnership among the Agency for Healthcare Research and Quality, the FDA, academia, the medical-products industry, and consumer groups. This partnership focuses on research and education that will advance the best use of medical products.

Dr. Califf has been married to Lydia Carpenter since 1974, and they have three children — Sharon Califf Boozer, a graduate of Elon College; Sam, a graduate student at the University of Colorado-Boulder; and Tom, a recent graduate of Duke University — and one grandchild. Dr. Califf enjoys golf, basketball, and listening to music.

C. Thomas Caskey, MD, FACP is Director-Elect and Chief Executive Officer-Elect and Chief Operating Officer of the Brown Foundation Institute of Molecular Medicine for the Prevention of Human Diseases (IMM), at the University of Texas Health Science Center at Houston.

Dr. Caskey was founding director of Houston-based Cogene Biotech Ventures and Cogene Ventures, venture capital funds supporting early-stage biotechnology and life sciences companies. The fund, founded in March 2000, invested in companies that utilize genome technology to enable drug discovery in high growth therapeutic specialties such as cancer, neurology and the metabolic diseases of obesity and diabetes.

Dr. Caskey has received numerous academic and industry-related honors. He is a member of the National Academy of Sciences and the Institute of Medicine. He has served as president of American Society of Human Genetics, the Human Genome Organization and The Academy of Medicine, Engineering and Science of Texas (TAMEST).

He previously served as Senior Vice President for Human Genetics and Vaccines Discovery at Merck Research Laboratories from 1994 to 2000 and as president of the Merck Genome Research Institute from 1998 to 2000.

His genetic research documented the universality of the genetic code, discovered the mechanism of peptide chain termination, identified the genetic basis of 10 major heritable diseases, opened the understanding of triplet repeat diseases (Fragile X, myotonic dystrophy and others), developed the STR method of DNA-based personal identification (now used worldwide) for forensic studies, and developed a viral vector vaccine for HIV.

He received the Distinguished Texas Geneticist Award from the Texas Genetics Society in 1998 and serves on Texas Governor Rick Perry's Council on Science and Biotechnology, which makes funding recommendations for the \$200 million Texas Emerging Technology Fund.

He served on the Intramural Human Genome Projects Special Review Committee, the National Institutes of Health, on the editorial boards of the Journal of the American Medical Association and Science and as editor of the Annual Review of Medicine. He has been a member of many medical societies and advisory boards throughout his career.

Dr. Caskey earned his medical degree from Duke University School of Medicine and his undergraduate degree from the University of South Carolina. He is Board certified in Internal Medicine, Clinical Genetics, Metabolic Diseases and Molecular Diagnostics.

He also serves on the boards of several corporations, including En Vivo, MDS Inc., Odyssey Thera, Argolyn Bioscience, and Metabolon. He

is a director of the Washington Advisory Group, which provides management and strategy consulting services for clients in academia, information technology, bio-technology, health care, manufacturing and natural resources.

P. Joan Chesney, MD, CM received her MD degree from McGill University in Montreal, Quebec, Canada. She completed her pediatric residency training at Strong Memorial Hospital in Rochester, NY and Johns Hopkins Hospital in Baltimore, MD. Her post-doctoral training included fellowships in both Microbiology and Pediatric Infectious Diseases at Johns Hopkins Hospital and in Pediatric Infectious Diseases at the Montreal Children's Hospital of McGill University. Formerly Director of the Pediatric Infectious Disease Divisions at the University of Wisconsin, Madison and the University of California, Davis, Dr. Chesney is currently Professor of Pediatrics at the University of Tennessee Health Science Center in Memphis, TN and Member in the St. Jude Children's Research Hospital Department of Infectious Diseases also in Memphis. She also serves as Associate Dean for St. Jude Academic Affairs at the University of Tennessee College of Medicine and is Director of the Academic Programs Office at St. Jude.

In Madison, WI, Dr. Chesney worked closely with Dr. Jeff Davis to determine the association of TSS with tampon use and with Dr. Merlin Bergdoll to identify TSST-1 and other factors involved in the Toxic-Shock Syndrome "outbreak" in 1980. In Memphis, TN, Dr. Chesney worked closely with colleagues in Memphis and at the CDC to clarify factors involved in the new third generation cephalosporin resistant pneumococcal "outbreak." Both experiences were documented in Discovery Channel programs as well as in scientific publications, presentations, senate subcommittee hearings and committee work for national specialty organizations, including the CDC, Infectious Disease Society of America (IDSA) and the American Academy of Pediatrics (AAP).

Dr. Chesney served on the IDSA Antibiotic Use & Clinical Trials Committee for six years and on the AAP Committee on Infectious Diseases (COID or Redbook Committee) for six years. Following five years as a member of the FDA Anti-infectives Drug Advisory Committee, she was appointed chair of the new Pediatric Advisory Committee. She served as chair of this committee from 3/1/99-6/30/05 and continues to serve as a consultant.

Current research interests include the pathogenesis and pathophysiology of bacterial toxin-mediated syndromes, the epidemiology and management of antibiotic resistant *Staphylococcal* infections, and the preparation of graduate students and both clinical and basic science fellows for successful careers in the biomedical sciences.

David DeMets, PhD is currently Professor and Chair of the Department of Biostatistics and Medical Informatics at the University of Wisconsin – Madison.

Since receiving his PhD in 1970, he has been very active in the design, conduct, and analysis of clinical trials in several disease areas. Following a post-doctoral appointment at the National Institutes of Health (1970–1972), he spent ten years (1972–1982) at the National Heart, Lung and Blood Institute at the National Institutes of Health where he became chief of a Biostatistics Research Branch. He has co-authored three texts, *Fundamentals of Clinical Trials*, *Data Monitoring in Clinical Trials: A Case Studies Approach* and *Data Monitoring Committees in Clinical Trials: A Practical Perspective*.

Dr. DeMets is a recognized international leader in statistical research and methods for the analysis of clinical trials. He has collaborated in the development of statistical methods for the sequential analysis of outcome data and the design of clinical trials. He has extensive national and international clinical trial experience and has served on and chaired numerous NIH and industry-sponsored Data Safety and Monitoring Committees for clinical trials in diverse disciplines. He served on the Board of Scientific Counselors of the National Cancer Institute and Board of Directors of the American Statistical Association, as well as having been President of the Society for Clinical Trials and President the Eastern North American Region (ENAR) of the Biometric Society. In addition he was Elected Fellow of the Society for Clinical Trials in 2006

Since 1990 Dr. DeMets has served on the following UW committees: Ad hoc Committee on Conflict of Interest (1992–1993); Tenure Track Promotions Committee (1995–1998) and Biomedical Industry Relations Committee (1996–1998). In addition he has served on the Search Committees for: UWCCC Director (1994–1997), Associate Dean for Research (Chair) (1995–1996), Associate Dean for Administration (1995–1996), Section of Cardiology Chief (1988–1999) and Preventive Medicine Chair (1999–2000), Medical School Dean Search Committee (2005–2006). Graduate School committees include the Committee on Training Research Ethics (Chair) 1993–1996 & 1998–2000 and the Health Sciences Information Technology Committee 1999–2003. He has also served on the following committees in the School of Medicine and Public Health: Medical Education and Research Committee (MERC) (2004–2007), UW Center for Women’s Health Advisory Board (2005–2008), Human Subjects Committee (1982–1987; 2002–2006).

Susan Desmond-Hellmann, MD, MPH is currently President of Product Development at Genentech; responsible for Medical Affairs, Regulatory Affairs, Product Development, Development Sciences and

Quality functions, as well as Business Development and Strategic Pipeline Development. Dr. Desmond-Hellmann has overseen the successful clinical development of 4 products at Genentech that have extended survival in cancer; Rituxan, Herceptin, Avastin, and Tarceva;. She currently oversees a pipeline with multiple oncology therapeutics, including approaches to apoptosis, Hedgehog antagonism, anti-CD20, and an inhibitor of HER2 dimerization.

In addition to her work at Genentech, Dr. Desmond-Hellmann is an Adjunct Associate Professor of Epidemiology and Biostatistics at the University of California, San Francisco (UCSF), and has also served as Assistant Professor, Hematology–Oncology. She spent two years as visiting faculty at the Uganda Cancer Institute studying AIDS and cancer, as well as two years in private practice before returning to research.

In 2004, 2003 and 2001, Dr. Desmond-Hellmann was named to FORTUNE magazine's Top 50 Most Powerful Women in Business list. In 2002, she was named to the US Department of Health and Human Services Advisory Committee on Regulatory Reform. Dr. Desmond-Hellmann was named to the Board of Directors of the Biotechnology Industry Organization (BIO) in 2001, where she now serves on the Board's Executive Committee. Since 1980, she has received many honors and awards for her work in oncology and AIDS research.

Dr. Desmond-Hellmann is board-certified in internal medicine and medical oncology and completed her clinical training at UCSF. Desmond-Hellmann holds bachelor and medical degrees from the University of Nevada, Reno, as well as a master's degree in epidemiology and biostatistics from the University of California, Berkeley, School of Public Health.

Susan Ellenberg, PhD is Professor of Biostatistics at HUP, University of Pennsylvania. Dr. Ellenberg's research interests have focused on issues in the design and analysis of clinical trials, and assessment of medical product safety. Particular areas of interest include efficient trial designs, interim monitoring and the operation of data monitoring committees, evaluation of surrogate endpoints, ethical issues in clinical research, and special issues in trials of cancer and AIDS therapies, and of vaccines. She serves as Associate Editor of Clinical Trials and of the Journal of the National Cancer Institute. Dr. Ellenberg is a Fellow of the American Statistical Association and the American Association for the Advancement of Science, and an elected member of the International Statistical Institute. She has served as President of the Society for Clinical Trials and the Eastern North American Region of the International Biometric Society, and has chaired the Statistics Section of the AAAS. Her recent book on clinical trials data monitoring committees, co-authored with Drs. Thomas Fleming (University of Washington) and David DeMets (University of

Wisconsin), was named WileyEurope Statistics Book of the Year for 2002.

Garret A. FitzGerald, MD studied Medicine at University College in Dublin (UCD), Statistics at both Trinity College in Dublin and the London School of Hygiene and Pharmacology at the Royal Postgraduate Medical School in London, the Max Planck Institute in Cologne and Vanderbilt University in Nashville. His doctoral work was on the development and application of biochemical indices of sympathoadrenal function, but his attention turned to prostaglandin biology almost 30 years ago.

Dr. FitzGerald rose to lead the Division of Clinical Pharmacology as the William Stokes Professor of Experimental Therapeutics at Vanderbilt before returning to Ireland where he was Chair of Medicine and Therapeutics at UCD where he founded the Center for Cardiovascular Science. He returned to the US as the Robinette Foundation Professor of Cardiovascular Medicine to establish a Center for Experimental Therapeutics at Penn and became the Elmer Bobst Professor and Chair of Pharmacology in 1996. Dr. FitzGerald established the Institute for Translational Medicine and Therapeutics in 2004 which will be the "academic home" for the recently funded Clinical and Translational Award which he led on behalf of Penn and its partner institutions.

Dr. FitzGerald's work was fundamental to the discovery of the cardioprotective properties of low dose aspirin. His group defined the dose dependent effects of aspirin on thromboxane and prostacyclin synthesis *in vivo*; the site of low dose aspirin action on platelets in the presystemic circulation and the pharmacodynamic interaction of traditional non-steroidal anti-inflammatory drugs like ibuprofen with aspirin. He was the first to show altered thromboxane formation in unstable angina and during therapeutic thrombolysis and provided the first proof of principle for use of antithrombotic drugs as adjuvants to thrombolytic drugs. He developed a matrix controlled release formulation which confined aspirin action to the presystemic circulation, sparing systemic vascular prostacyclin: this preparation was effective in the primary prevention of myocardial infarction in a randomized trial. His work both influenced the dosing regimens and patient selection for the randomized trials which established the cardioprotective efficacy of low dose aspirin.

Dr. FitzGerald was the first to discover the physiological importance of COX-2 in the synthesis of prostacyclin and to predict that selective inhibitors of this enzyme might confer cardiovascular hazard. He developed a series of mouse models that afforded proof of principal for such a mechanism, which is consistent with the outcome of the placebo controlled trials which revealed the cardiovascular hazard of such drugs. More recently, he has shown the potential of mPGES-1

inhibitors to avoid this hazard and perhaps confer cardiovascular benefit by enhancing production of prostacyclin.

Aside from these contributions, Dr. FitzGerald's laboratory was the first to develop mass spectrometric assays for individual isoprostanes and contributed substantially to their emergence as quantitative indices of lipid peroxidation *in vivo*. His group also was the first to discover and characterize a molecular clock in the vasculature. His work has revealed unexpected roles for the clock in both cardiovascular and metabolic function.

Amongst the distinctions received by Dr. FitzGerald are the Robert Boyle and William Harvey Medals for Scientific Excellence and the Cameron Prize for Practical Therapeutics. He has received honorary degrees from Dublin and Edinburgh and currently serves on strategy committees of the Institute of Medicine, the NHLBI, the AHA, Science Foundation Ireland, the Dublin Molecular Medicine Center, the NHS, the Wellcome Trust, the MRC (UK) and the Research Assessment Exercise of the UK Government.

Alfred G. Gilman, MD, PhD was born in New Haven, Connecticut in 1941. He received his BS (summa cum laude) in Biochemistry in 1962 from Yale University, and his MD and PhD in Pharmacology in 1969 from Case Western Reserve University. Dr. Gilman received further training as a Pharmacology Research Associate in the Laboratory of Biochemical Genetics at the National Institutes of Health (1969–71).

In 1971 Dr. Gilman began a 10-year stay at the University of Virginia in Charlottesville. His positions included Assistant Professor of Pharmacology (1971–1973), Associate Professor of Pharmacology (1973–1977), Professor of Pharmacology (1977–1981), and Director of the Medical Scientist Training Program (1978–1981). Dr. Gilman became Chairman of the Department of Pharmacology at the University of Texas Southwestern Medical Center at Dallas in 1981, a position he held until 2006. He was named a Regental Professor in 1995. In addition he is director of the Cecil H. and Ida Green Comprehensive Center for Molecular, Computational, and Systems Biology and in 2004 was appointed Interim Dean of Southwestern Medical School; he accepted this position permanently in 2005. In 2006 he was named the Executive Vice President for Academic Affairs and Provost in addition to his title of Dean. Dr. Gilman holds the Raymond and Ellen Willie Distinguished Chair of Molecular Neuropharmacology, the Nadine and Tom Craddick Distinguished Chair in Medical Science, and the Atticus James Gill, PHD Chair in Medical Science.

Dr. Gilman discovered, characterized, and purified a set of guanine nucleotide-binding regulatory proteins termed G proteins. His observations provided for the first time a firm molecular basis for

understanding certain signal transduction processes present throughout nature. He was also the primary editor (in 1980, 1985, and 1990) of the best known textbook of Pharmacology, *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. In 2000 Dr. Gilman established the Alliance for Cellular Signaling (AfCS) – a multidisciplinary, multi-institutional program to study the network properties of cellular signaling systems. Dr. Gilman has received a number of honors and awards for this work including, among others, The Gairdner Foundation International Award (1984); Richard Lounsbery Award (The National Academy of Sciences, 1987); American Association of Medical Colleges Award for Distinguished Research in the Biomedical Sciences (1988); Albert Lasker Basic Medical Research Award (1989); Louisa Gross Horwitz Prize (Columbia University, 1989); Passano Foundation Award (1990); American Heart Association Basic Science Research Prize (1990); Louis S. Goodman and Alfred Gilman Award in Drug Receptor Pharmacology (American Society of Pharmacology & Experimental Therapeutics, 1990); Waterford Award (Research Institute of Scripps Clinic, 1990); Steven C. Beering Award (Indiana University School of Medicine, 1990); and The Nobel Prize in Physiology or Medicine (1994). In addition, Dr. Gilman was elected to membership in the National Academy of Sciences (1986); The American Academy of Arts & Sciences (1988); and the Institute of Medicine of the National Academy of Sciences (1989), and has received honorary degrees from The University of Chicago (1990), Case Western Reserve University (1995), Yale University (1997), and the University of Miami (1999).

Robert A. Goldstein, MD, PhD is the Chief Scientific Officer for the Juvenile Diabetes Research Foundation International (JDRF) where he is responsible for developing and guiding research programs of the foundation. After receiving his undergraduate degree from Brandeis University, he received his MD from Jefferson Medical College, his PhD (in Microbiology/Immunology) from George Washington University and his MBA from the Stern School of Business, New York University. Before joining JDRF in 1997, he was Director of the Division of Allergy, Immunology and Transplantation at the National Institute of Allergy and Infectious Diseases, NIH. Dr. Goldstein represents JDRF at the NIH Diabetes Mellitus InterAgency Coordinating Committee (DMICC) and at the Autoimmune Diseases Coordinating Committee. He serves on the UK National Health Service- National Institute for Health Research Advisory Board, and on the Scientific Advisory Board of Fondazione Telethon in Italy. He has represented JDRF at various stem cell forums, including the International Stem Cell Forum, the US National Academy of Sciences, the US Presidential Commission on Bioethics, the California Institute of Regenerative Medicine; the American Association for the Advancement of Science, and the United States Senate.

Leroy E. Hood, MD, PhD is President, Institute for Systems Biology. Dr. Hood's research has focused on fundamental biology (immunity, evolution, genomics) and on bringing engineering to biology through the development of five instruments — the DNA and protein sequencers and synthesizers and the ink-jet oligonucleotide synthesizer (making DNA arrays) — for deciphering the various types of biological information (DNA, RNA, proteins and systems). These instruments constitute the technological foundation for modern molecular biology and genomics. He has applied these technologies to diverse fields including immunology, neurobiology, cancer biology, molecular evolution and systems medicine.

Dr. Hood has been driven by the conviction that the needs of frontier biology should drive the selection of technologies to be developed, and once a new technology is developed these technologies can revolutionize biology and medicine. His professional career began at Caltech where he and his colleagues pioneered the four instruments mentioned above. In particular, the DNA sequencer has revolutionized genomics by allowing the rapid automated sequencing of DNA, which played a crucial role in contributing to the successful mapping of the human genome during the 1990s. He applied all of these technologies to the study of molecular immunology (and discovered many of the fundamental mechanisms for antibody diversity) and neurobiology (he cured in mice the first neurological disease by gene transfer). In the late 1980s he realized that to really understand immunology would require a systems approach, and began thinking about systems biology.

In 1992, Dr. Hood moved to the University of Washington as founder and Chairman of the cross-disciplinary Department of Molecular Biotechnology (MBT) and developed the ink-jet oligonucleotide synthesizer which synthesized DNA chips. At MBT he initiated systems studies on cancer biology and prion disease. In 2000, he co-founded the Institute for Systems Biology in Seattle, Washington to more effectively continue pioneer systems approaches to biology and medicine. Here he has contributed seminal papers to delineating the systems approach to biology and disease and to pioneer developing new technologies (microfluidics/nanotechnology and molecular imaging) in collaboration with colleagues at Caltech and UCLA, that are establishing the framework for medicine evolving from its current reactive mode to a predictive, preventive, personalized and participatory mode (P4 medicine) over the next 5–20 years.

Dr. Hood was awarded the Lasker Prize in 1987 for his studies on the mechanism of immune diversity. Dr. Hood was also awarded the 2002 Kyoto Prize in Advanced Technology for the development of the five different instruments. He received the 2003 Lemelson–MIT Prize for Innovation and Invention — for the development of the DNA sequencer. Most recently, Dr. Hood's lifelong contributions to biotechnology have earned him the prestigious 2004 Biotechnology Heritage Award, and for his pioneering efforts in molecular diagnostics

the Association for Molecular Pathology (AMP) Award for Excellence in Molecular Diagnostics. In 2006 he received the Heinz Award in Technology, the Economy and Employment for his extraordinary breakthroughs in biomedical science at the genetic level. Dr. Hood has received 14 honorary degrees from Institutions such as Johns Hopkins, UCLA, and Whitman College. He has published more than 600 peer-reviewed papers, received 14 patents, and has co-authored textbooks in biochemistry, immunology, molecular biology, and genetics, and is just finishing a text book on systems biology. He is a member of the National Academy of Sciences, the American Philosophical Society, the American Association of Arts and Sciences, and the Institute of Medicine. Dr. Hood has also played a role in founding more than 14 biotechnology companies, including Amgen, Applied Biosystems, Systemix, Darwin and Rosetta. He is currently pioneering systems medicine and the systems approach to disease.

Peter Barton Hutt is a senior counsel in the Washington, D.C. law firm of Covington & Burling LLP specializing in food and drug law. He graduated from Yale College and Harvard Law School and obtained a Master of Laws degree in Food and Drug Law from NYU Law School. Mr. Hutt served as Chief Counsel for the Food and Drug Administration during 1971–1975. He is the co-author of the casebook used to teach food and drug law throughout the country, and has published more than 175 book chapters and articles on food and drug law and health policy. He teaches a full course on this subject during Winter Term at Harvard Law School and has taught the same course during Spring Term at Stanford Law School. Mr. Hutt has been a member of the Institute of Medicine since it was founded in 1971. He serves on academic, philanthropic, and venture capital advisory boards, and the boards of startup biotechnology companies. He recently served on the Panel on the Administrative Restructuring of the National Institutes of Health and the Working Group to Review Regulatory Activities within the Division of AIDS of the National Institute of Allergy and Infectious Diseases, and is a member of the Board of Directors of the AERAS Global TB Vaccine Foundation. He was named by The Washingtonian magazine as one of Washington's 50 best lawyers (out of more than 40,000) and as one of Washington's 100 most influential people; by the National Law Journal as one of the 40 best health care lawyers in the United States; and by European Counsel as the best FDA regulatory specialist in Washington, DC. In June 2003, Business Week referred to Mr. Hutt as the "unofficial dean of Washington food and drug lawyers." In naming Mr. Hutt in September 2005 as one of the eleven best food and drug lawyers, the Legal Times also referred to him as "the dean of the food-and-drug bar." In April 2005, Mr. Hutt was presented the FDA Distinguished Alumni Award by FDA Commissioner Crawford. In May 2005, the Foundation for Biomedical Research gave him the Lifetime Achievement Award for research advocacy.

Evan Kharasch, MD, PhD is the Russell D. and Mary B. Shelden Professor of Anesthesiology, and Director of the Division of Clinical and Translational Research, Department of Anesthesiology, Washington University in St. Louis.

He received his PhD in Pharmacology and MD at Northwestern University in Chicago, and anesthesiology training at the University of Washington, where he subsequently joined the faculty in 1988. He ultimately achieved the rank of Professor of Anesthesiology and Medicinal Chemistry (Adjunct), and Vice-Chair of Anesthesiology. He is a basic, translational and clinical pharmacologist, with research interests including the pharmacology of anesthetic and analgesic drugs; drugs of abuse and their treatments; laboratory, clinical and non-invasive assessment of drug metabolism and drug interactions; clinical optimization of drug use; and mechanisms of interindividual variability in drug disposition and response, including pharmacogenetics and drug interactions. He has published more than 170 original articles, reviews and book chapters. At the University of Washington, he was also the Associate Program Director of the General Clinical Research Center, and the Assistant Dean for Clinical Research. He joined Washington University in St Louis in 2005, to continue his investigational activities and to create the Division of Clinical and Translational Research. In addition to research activities, his administrative and organizational interests include clinical research investigator training, quality assurance in clinical research, research information management, quality and improvement in regulatory aspects of clinical research, and harmonization of research compliance procedures. He is an Editor of the journal *Anesthesiology*, reviews for numerous other journals, and has served on several NIH and VA Study Sections. He is also a practicing anesthesiologist, with interests ranging from outpatient to high-risk anesthesia.

Sangtae "Sang" Kim, PhD is the inaugural Donald W. Feddersen Distinguished Professor of Mechanical Engineering and Distinguished Professor of Chemical Engineering at Purdue. The Feddersen Distinguished Professorship is supported by a substantial endowment targeting emerging opportunities at the interface of engineering and information technologies. Sang's recently completed eight-year voyage beyond the ivory tower spanned both the public (NSF Division Director at the launch of the Cyberinfrastructure Division) and private (VP level positions heading R&D IT in the pharmaceutical industry at the inflection point of the genomic revolution) sectors. During 1983–1997, Sang was a faculty member in Chemical Engineering at the University of Wisconsin-Madison, where he engaged in mathematical and computational methods for microhydrodynamics (now more commonly known as microfluidics). His computational insights into "hydrodynamic

steering” played an influential role in 1994–1995 in the development of fluidic self assembly (FSA), the novel process employed today for manufacturing of low-cost RFID (radio frequency) tags. Sang is a member of the National Academy of Engineering and a fellow of the American Institute of Medical and Biological Engineers. His research citations include the 1993 Allan P. Colburn Award of the American Institute of Chemical Engineers, the 1992 Award for Initiatives in Research from the National Academy of Sciences and a Presidential Young Investigator award from NSF in 1985. His 1991 treatise, *Microhydrodynamics*, is considered a classic in that field and was recently selected by Dover Publications for its reprint series. A native of Seoul, but a product of the “K-11” public schools of Montreal, Sang received concurrent BSc and MSc degrees (1979) from Caltech and a PhD (1983) from Princeton.

Julia Lane, PhD is a Senior Vice President, Economics, Labor and Population Studies at the National Opinion Research Center at the University of Chicago and a Senior Research Fellow at the US Bureau of the Census.

From August 2004 to December 2005, she was an Economics Program Director at the National Science Foundation. In that capacity, she was charged with coordinating the cyberinfrastructure strategy of the Social, Behavioral and Economic Sciences Directorate.

From January 2000 to August 2004, Dr. Lane was the Director of the Employment Dynamics Program at the Urban Institute. Together with her co-investigators, John Abowd and John Haltiwanger, she received several major grants during that period. These included a \$1.4 million grant from the Alfred P. Sloan Foundation to study the impact of economic turbulence on firms and workers; a \$700,000 grant from the Rockefeller and Sage foundations, together with the Department of Health and Human Services to examine the long run dynamic interactions of workers and firms in the low-wage labor market, and a \$4.1 million grant from the National Science Foundation to develop a new dynamic employer-household database that enhance the social data infrastructure.

From August 1990 to December 1999, Dr. Lane was an Assistant, Associate, and Full Professor of Economics at American University. During the period 1997–2004, Dr. Lane initiated and founded (with John Abowd and John Haltiwanger) the Longitudinal Employer-Household Dynamics Program at the US Census Bureau. This program was the first large-scale linked employer-employee dataset in the United States, and has evolved into a permanent Census Bureau program (<http://lehd.dsd.census.gov>). She was also responsible for drafting and finalizing Internal Revenue Service regulations changes that permitted established the legal basis for a federally based

employer-employee dataset as well as the state based employer-employee dataset.

Dr. Lane has authored or co-edited four books, and published over 50 articles. She has consulted with and worked with a number of national and international agencies, including the World Bank, the British Economic and Social Research Council, the National Academies of Sciences, and a variety of government agencies in the United States, as well as Madagascar, Morocco, New Zealand, Tunisia, Malaysia and Mexico. She has been invited to present or give keynote speeches at conferences, universities and research institutes in Austria, Australia, Canada, Denmark, England, France, Germany, Italy, the Netherlands, New Zealand, Norway, Spain and Sweden, as well as the United States.

Many awards have been bestowed upon Dr. Lane. Two of her most recent awards are the National Science Foundation Director's award for program management excellence and the 2004 National Association of State Workforce Agencies Vladimir Chavrid award for excellence in the field of Labor Market Information (LMI) and Employment Security operations research. She is most proud of being the first recipient of the Faculty Member of the Year Award from the American University Student Confederation in 1996.

Dr. Lane is a native of England, but her elementary, intermediate and high school education were in New Zealand. Her BA was received from Massey University, New Zealand, in 1976; her MA in Statistics and her PhD in Economics were received from the University of Missouri in 1982. She speaks Swedish, German and French.

Cato T. Laurencin, MD, PhD, is the Lillian T. Pratt Distinguished Professor and Chairman of the Department of Orthopaedic Surgery at the University of Virginia. He serves as Orthopaedic Surgeon-in-Chief of the University of Virginia Health System. Dr. Laurencin is Professor of Chemical Engineering and Professor of Biomedical Engineering at the school. In addition, he has been designated a University Professor by the President of the University of Virginia.

Dr. Laurencin earned his BSE in Chemical Engineering from Princeton University, his MD from the Harvard Medical School where he graduated *Magna Cum Laude* and his PhD in Biochemical Engineering/Biotechnology from the Massachusetts Institute of Technology where he was a Hugh Hampton Young Scholar.

Dr. Laurencin completed the Harvard University Orthopaedic Surgery Residency Program, and was Chief Resident in Orthopaedic Surgery at the Beth Israel Hospital, Harvard Medical School. He subsequently completed a clinical fellowship in Shoulder Surgery and Sports Medicine at the Hospital for Special Surgery, Cornell Medical College in New York.

Board certified in orthopaedic surgery, Dr. Laurencin is a Fellow of the American College of Surgeons, a Fellow of the American Surgical Association, and a Fellow of the American Academy of Orthopaedic Surgeons. He has been the recipient of the prestigious American Orthopaedic Association American, British, and Canadian (ABC) Traveling Fellowship, and has been an instructor in shoulder surgery at the American Academy of Orthopaedic Surgery's Orthopaedic Learning Center. For his clinical work, Dr. Laurencin was named as one of the Top 101 Doctors in America by Black Enterprise Magazine, and has been named to America's Top Doctors and America's Top Surgeons.

Dr. Laurencin is an elected member of the Institute of Medicine of the National Academy of Sciences.

Dr. Laurencin has been involved in numerous service activities at the National and International level. He was Speaker of the House of Delegates of the National Medical Association, and is currently Chair of the Steering and Oversight Committee (Board of Directors) of the W. Montague Cobb/National Medical Association Health Institute. He is a member of the Science Advisory Board of the FDA, the National Science Foundation's Advisory Committee for the Directorate of Engineering, and has been a member of the National Advisory Council for Arthritis, Musculoskeletal, and Skin Diseases at NIH. In addition, Dr. Laurencin is currently a member of the Roundtable on Evidence Based Medicine of the Institute of Medicine.

Dr. Laurencin's other academic interests are in the areas of tissue engineering, biomaterials, drug delivery and nanotechnology. Honored at the White House, Dr. Laurencin received the Presidential Faculty Fellowship Award from President William Clinton in recognition of his research work bridging medicine and engineering. Dr. Laurencin is a Fellow of the American Institute for Medical and Biological Engineering, and an International Fellow in Biomaterials Science and Engineering. He is the recipient of the William Grimes Award for Excellence in Chemical Engineering from the American Institute of Chemical Engineers and the Leadership in Technology Award from the New Millennium Foundation for his work in Tissue Engineering. Most recently, Dr. Laurencin was awarded the Clemson Award (from the Society for Biomaterials) for Outstanding Contributions to the Biomaterials Literature, and the Nicolas Andry Award (from the Association of Bone and Joint Surgeons) for outstanding Orthopaedic Research.

Jeffrey M. Leiden, MD, PhD is a partner at Clarus Ventures, LLC, a life-sciences venture capital firm with headquarters in Cambridge, MA. Dr. Leiden received his BA, PHD, and PhD degree in Virology from the University of Chicago. He completed his residency in Internal Medicine and his fellowship in Cardiology at the Brigham and Women's Hospital, Harvard Medical School. Between 1985 and 1992 Dr. Leiden

was an Assistant and Associate Professor in the Departments of Medicine and Microbiology/Immunology and an Assistant/Associate Investigator in the Howard Hughes Medical Institute at the University of Michigan. From 1992 to 1999, Dr. Leiden was the Frederick H. Rawson Professor of Medicine and Pathology and Chief of the Section of Cardiology at the University of Chicago. In July 1999, Dr. Leiden moved to Harvard as the Elkan R. Blout Professor of Biological Sciences, Professor of Medicine and Director of the Center for the Prevention of Cardiovascular Disease at the Harvard School of Public Health and the Harvard Medical School. Dr. Leiden's research interests include the transcriptional regulation of cardiovascular development and gene therapy approaches for human cardiovascular disease. He has published more than 130 papers and 25 invited book chapters and review articles in these areas.

Dr. Leiden's business experience began in the 1990s when he founded several biotechnology companies including Cardiogene Inc., a cardiovascular gene therapy company that was acquired by Boston Scientific in 1999. He was elected to the Board of Directors of Abbott Laboratories in 1999 and served as President and Chief Operating Officer of Abbott from 2000–2006, where he was responsible for directing all aspects of Abbott's global pharmaceutical business. He currently serves as Chairman of the Board of Variation Biotechnology Inc, and as a non-executive Director of Shire, plc. Dr. Leiden was elected to Phi Beta Kappa, Alpha Omega Alpha, The American Society for Clinical Investigation, and The American Association of Physicians and served on the Board of Scientific Counselors of the National Heart Lung and Blood Institute of the NIH between 1994 and 1999. In 1999, he was elected President of the American Society of Clinical Investigation. He is a fellow of the American Academy of Arts and Sciences and an elected member of the Institute of Medicine of the National Academy of Sciences.

J. Glenn Morris, Jr., MD, MPH, TM is Director of the newly established Emerging Pathogens Institute at the University of Florida, Gainesville. From 2000–2007 he served as Chairman of the Department of Epidemiology and Preventive Medicine at the University of Maryland School of Medicine, Baltimore (UMB), and from 2005–2007 was interim dean of the UMB School of Public Health.

Dr. Morris received his MD degree and a masters degree in public health and tropical medicine from Tulane University, New Orleans. He served as an Epidemic Intelligence Service Officer in the Division of Enteric Diseases at the Centers for Disease Control in Atlanta from 1979–1981. He is board-certified in both internal medicine and infectious diseases. Dr. Morris has authored over 60 textbook chapters and symposium proceedings and over 180 articles in peer-reviewed journals. He has had continuous federal grant funding since 1984; his scholarly contributions were recognized by election to the American

Society for Clinical Investigation in 1996. He has served on four National Academy of Sciences expert committees dealing with food safety, and currently serves on the Institute of Medicine's Food and Nutrition Board. From 1994–1996, he worked with the Food Safety Inspection Service, US Department of Agriculture, on the preparation of the Pathogen Reduction/HACCP regulations. In 2005, he was awarded the James D. Bruce Memorial Award for Distinguished Contributions in Preventive Medicine by the American College of Physicians in recognition of his work in food safety.

Dr. Morris has maintained a strong research interest in the area of emerging pathogens: he has an active, NIH-funded laboratory working in the area of molecular genetics and molecular epidemiology; is involved in hospital studies looking at emergence of resistant microorganisms; has worked extensively with clinical, laboratory, and environmental issues related to harmful algal blooms; and has served as co-PI of the CDC Emerging Infections Program sentinel surveillance site (FoodNet) in Maryland. Effective September 1, 2007, he will become the first Director of the University of Florida Emerging Pathogens Institute, established by an initial \$56 million appropriation from the Florida legislature.

Philip Needleman, PhD, MS, BS is the former Chief Scientific Officer and Senior Executive Vice President of Pharmacia Corporation who retired (2003) following the Pfizer acquisition. Following the merger of Monsanto and Pharmacia (2000), he became Chairman, Research and Development of Pharmacia. He joined Monsanto in 1989 as Chief Scientist and became President of Searle Pharmaceutical Company (1993). He received his B.Sc. (Pharmacy, 1960) and M.Sc. (Pharmacology, 1962) from the Philadelphia College of Pharmacy and Science; received his PhD (Pharmacology, 1964) from U. Maryland Medical School; and was a post-doctoral fellow at Washington University Medical School. He joined the faculty (1967) and rose to Chairman of the Department of Pharmacology (1976 to 1989). During that time, he was selected Basic Science Teacher of the Year five times. He served as Associate Dean for Special Projects at Washington University Medical School (St Louis) in 2004. He was elected a member of the National Academy of Sciences (NAS, 1987) and the Institute of Medicine (1993). At the NAS he chaired the Pharmacology-Physiology section (2001–2004) and was elected (2004) to the NAS Council (board of trustees). He is a member of the Washington University Board of Trustees. In St Louis he is a member of the boards of the St Louis Science Center, the Barnes Jewish Hospital Board, Plant and Life Sciences Coalition, and the Donald Danforth Plant Science Center.

In 2002, he was appointed Special Advisor to the President for Research and Development at Ben-Gurion University of the Negev, and has joined the University's Advisory committee for the creation of a National Institute for Biotechnology in the Negev.

Needleman has garnered numerous honors, including the: John Jacob Abel Award of the American Pharmacology Society (1974); Research Achievement Award from the American Heart Association (1988); Washington University's Distinguished Faculty Award (1987), Second Century Award from the medical school (1994), and honorary doctorate degree (1999); C. Chester Stock Award Lectureship at Memorial-Sloan Kettering Cancer Center (2001); the Industrial Research Institute Medal (2001); the American Society of Experimental Therapeutics award; and in 2005 the NAS Award for the Industrial Application of Science.

Robert M. Nerem, PhD is Professor and Director, Parker H. Petit Institute for Bioengineering and Bioscience, Georgia Institute of Technology. Dr. Nerem joined Georgia Tech in 1987 as the Parker H. Petit Distinguished Chair for Engineering in Medicine. He currently serves as the Director of the Parker H. Petit Institute for Bioengineering and Bioscience. In addition he serves as the Director of the Georgia Tech/Emory Center (GTEC) for the Engineering of Living Tissues, an NSF-funded Engineering Research Center. He received his PhD in 1964 from Ohio State University and joined the faculty there in the Department of Aeronautical and Astronautical Engineering, being promoted to Professor in 1972 and serving from 1975–1979 as Associate Dean for Research in the Graduate School. From 1979 to 1986 he was Professor and Chairman of the Department of Mechanical Engineering at the University of Houston. Professor Nerem is the author of more than 200 publications. He is a past President of the International Union for Physical and Engineering Sciences in Medicine (1991–1994) and also a past President of the International Federation for Medical and Biological Engineering (1988–1991). In addition, he is a past Chairman of the US National Committee on Biomechanics (1988–1991), and he is a Fellow and was the founding President (1992–1994) of the American Institute of Medical and Biological Engineering (AIMBE). He is past President of the Tissue Engineering Society International (2002–2004), and was a part-time Senior Advisor for Bioengineering in the new National Institute for Biomedical Imaging and Bioengineering at the National Institutes of Health (2003–2006). He is Fellow, American Association for the Advancement of Science; Fellow, Council of Arteriosclerosis, American Heart Association; Fellow, American Physical Society; and Fellow, American Society of Mechanical Engineers (ASME). He was Technical Editor of the ASME Journal of Biomechanical Engineering (1988–1997). In 1989 he received the H.R. Lissner Award from ASME and in 2002 the Pierre Galletti Award from AIMBE. In 1988 Professor Nerem was elected to the National Academy of Engineering (NAE), and he served on the NAE Council for six years (1998–2004). In 1992 he was elected to the Institute of Medicine of the National Academy of Sciences and in 1998 a Fellow of the American Academy of Arts and Sciences. In March 1990 Professor Nerem was presented with an honorary doctorate from the University

of Paris, and in 1994 he was elected a Foreign Member of the Polish Academy of Sciences. In 1998 he was made an Honorary Fellow of the Institution of Mechanical Engineers in the United Kingdom, in 2004 he was elected an honorary foreign member of the Japan Society for Medical and Biological Engineering, and in 2006 a Foreign Member of the Swedish Royal Academy of Engineering Sciences. Professor Nerem serves on the scientific advisory board of AtheroGenics, Inc and Tengion, Inc. Research interests include atherosclerosis, biomechanics, cardiovascular devices, cellular engineering, vascular biology, and tissue engineering and regenerative medicine.

Dale Nordenberg, MD is a Managing Director in the Healthcare Industry Advisory practice at Pricewaterhouse Coopers (PwC). As a member of the Enterprise Transformation Group, he works with healthcare and life science companies and institutions to facilitate strategic and operational improvement. Prior to starting at PwC in September 2007, Dr. Nordenberg served as the Associate Director and Chief Information Officer for the National Center for Infectious Diseases (NCID) at the CDC from 2002-2007. During his last several months at the CDC, Dr. Nordenberg was responsible for writing the CDC Information Technology strategic plan.

As the Associate Director and Chief Information Officer for the National Center for Infectious Diseases at the CDC Dr. Nordenberg was responsible for the informatics activities at the Agency's infectious disease center which included the development of critical infrastructure to support surveillance and response, as well as epidemiologic and laboratory/genomics research. During this time, Dr. Nordenberg developed and implemented an operational model that integrated the NCID subject matter and technology communities to deliver collaboratively designed systems and infrastructure. He works closely with national associations in the health care arena to build coalitions that promote the adoption of community-based interoperable information infrastructures for health care across both clinical and public health arenas. An area of particular interest is open innovation and Dr. Nordenberg has facilitated the development and funding of projects that leverage communities and networks to more effectively develop national infrastructure and information exchange such as the development of a national network of public health laboratories.

Dr. Nordenberg has worked with the Office of the National Coordinator for Health Information Technology, which included a detail to this Department of Health and Human Services Office, to promote development of national health information exchange among the children's health care community.

He participates in numerous informatics and scientific working groups and speaks widely in the area of informatics and health care both domestically and internationally. Dr. Nordenberg has a particular

interest in China where he has had numerous opportunities to live and work since the early 1980s and as a consequence is a fluent speaker of Mandarin Chinese.

Dr. Nordenberg maintains his clinical expertise in pediatrics by working regularly in the emergency department at Children's Health Care of Atlanta. He has been a board member of the Coventry of Georgia HMO since 1999.

Prior to his work at the CDC, Dr. Nordenberg worked in the academic and private sectors. In the academic sector, he established and directed the Office of Medical Informatics for Emory's Children Center/Department of Pediatrics. In the private sector, he led the development of Verisign Affiliates in Latin America and Asia. Dr. Nordenberg is a board certified pediatrician. He received a BS in Microbiology from the University of Michigan, his medical degree from Northwestern University and completed his training in pediatrics at McGill University, Montreal Children's Hospital. He completed his fellowship in epidemiology and public health in the Epidemic Intelligence Services Program at the Centers for Disease Control.

J. Marc Overhage, MD, PhD is President and CEO of the Indiana Health Information Exchange, director of medical informatics at the Regenstrief Institute, Inc., and a professor of medicine at the Indiana University School of Medicine.

He has spent over 25 years developing and implementing scientific and clinical systems and evaluating their value. Working with Dr. Clement McDonald, one of the pioneers of medical informatics, he has created an electronic patient record (called the Indiana Network for Patient Care) containing data from many sources including laboratories, pharmacies and hospitals in central Indiana. The system currently connects nearly all acute care hospitals in central Indiana and includes inpatient and outpatient encounter data, laboratory results, immunization data and other selected data. In order to create a sustainable financial model, he helped create the Indiana Health Information Exchange, a not-for-profit corporation. Over the last five years, he has played a significant regional and national leadership role in advancing the policy, standards, financing and implementation of health information exchange.

Dr. Overhage is also an expert in clinical decision support including inpatient and outpatient computerized physician order entry and the underlying knowledge bases to support them.

Dr. Overhage is a fellow of the American College of Medical Informatics and the American College of Physicians. He received the Davies Recognition Award for Excellence in Computer-Based Patient Recognition for the Regenstrief Medical Record System.

Dr. Overhage received his BA, with High Honors, in Physics from Wabash College and his PhD in Biophysics and MD from Indiana University School of Medicine. Dr. Overhage was a resident in internal medicine, a medical informatics and health services research fellow and then chief medical resident at the Indiana University School of Medicine. After completing informatics fellowship training, he served as an information advisor at Eli Lilly and Company and then joined the Regenstrief Institute.

Jim E. Riviere, DVM, PhD is the Burroughs Wellcome Fund Distinguished Professor of Pharmacology; Director, Center for Chemical Toxicology Research and Pharmacokinetics, College of Veterinary Medicine; and Director of the Biomathematics Program of the College of Physical and Mathematical Sciences, North Carolina State University (NCSU) in Raleigh NC. He is an elected member of the Institute of Medicine of the National Academies, serves on its Food and Nutrition Board, and is a fellow of the Academy of Toxicological Sciences. Dr. Riviere received his BS (summa cum laude) and MS degrees from Boston College and his DVM and PhD in pharmacology from Purdue University. He is a member of Phi Beta Kappa, Phi Zeta and Sigma Xi, and has served on the Science Board of the Food and Drug Administration. His honors include the 1999 O. Max Gardner Award from the Consolidated University of North Carolina, the 1991 Ebert Prize from the American Pharmaceutical Association, the Harvey W. Wiley Medal and FDA Commissioner's Special Citation, and the Lifetime Achievement Award from the European Association of Veterinary Pharmacology and Toxicology. He is the Editor of the *Journal of Veterinary Pharmacology and Therapeutics*, and co-founder and co-director of the USDA Food Animal Residue Avoidance Databank (FARAD) program. He has served as an officer in various Specialty Sections of the Society of Toxicology, and has served on the Editorial Boards of various toxicology, pharmacology and veterinary journals. He has published over 400 full-length research papers and chapters, holds five US Patents, and has authored/edited 10 books in pharmacokinetics, toxicology and food safety. His current research interests relate to applying biomathematics to problems in toxicology, including the risk assessment of chemical mixtures, pharmacokinetics, absorption of drugs and chemicals across skin, and the food safety and pharmacokinetics of tissue residues in food producing animals.

Eve E. Slater, MD, FACC is a Phi Beta Kappa graduate of Vassar College and an Alpha Omega Alpha graduate of Columbia University's College of Physicians & Surgeons. She completed internship and residency at the Massachusetts General Hospital (MGH) and is board certified in both internal medicine and cardiology.

In 1976, Dr. Slater became the first woman Chief Resident in Medicine in the 165-year history of MGH. From 1977 through 1982, she served as Chief of the Hypertension Unit at MGH and was Assistant Professor of Medicine at Harvard Medical School. She directed research funded by the NIH and the AHA, published on biochemical mechanisms involved in blood pressure control and diseases of the aorta, was active in patient care, and taught extensively. She continued clinical teaching as Adjunct Associate Clinical Professor of Medicine at Columbia (1983–2002) and was reappointed as Associate Clinical Professor of Medicine in 2005.

She joined Merck Research Laboratories (MRL) in 1983 as Senior Director of Biochemical Endocrinology, responsible for the endocrine, atherosclerosis, and receptor molecular biology teams; her research focused on receptor signal transduction. Dr. Slater became head of regulatory affairs in 1988, Vice President of Clinical and Regulatory Development in 1990, and Senior Vice President in 1994; the first woman to attain both ranks in MRL. In 2001, she was named Senior Vice President of MRL External Policy and Vice President, Corporate Public Affairs. Dr. Slater supervised worldwide regulatory activities for all Merck medicines and vaccines, which included responsibility for FDA and international Agency liaison, worldwide NDA submissions, product labeling, quality assurance and pharmacovigilance. Drugs approved during her tenure included major medicines to treat hypercholesterolemia, hypertension, osteoporosis, asthma, arthritis, prostate disease, and vaccines for chicken pox and h. influenza. She was responsible for the rapid approval of Crixivan, to treat HIV infection in 42 days, one of the shortest in FDA history. During her tenure, there were no FDA-mandated safety labeling changes. Additionally, Dr. Slater managed the Merck Manual, the Geriatrics Manual, and the Home Edition and was also responsible for OTC clinical development, as part of Johnson & Johnson–Merck Consumer Pharmaceuticals. The size of Dr. Slater's regulatory team tripled to over 600 individuals during her tenure. She served on the International Conference on Harmonization Subcommittee on the Structure and Content of Clinical Studies Reports (chair), and on both the Regulations Advisory (chair) and Policy Boards for the UK Centre for Medicines Research. She was a member of the US Keystone National Policy Dialogue on HIV, a founding member of the Collaborative Forum for HIV Research, and was named to the NIH Office of AIDS Research Advisory Council. She was a trustee of the Foundation of the University of Medicine and Dentistry of New Jersey and a member of the Board of the Liberty Science Center.

She was named by President George W. Bush as Assistant Secretary for Health (ASH), US Department of Health and Human Services, joining HHS shortly after the September 11, 2001 attack on America and received Senate confirmation to this position on January 25, 2002, thereby becoming America's first woman ASH. There she served HHS Secretary Tommy G. Thompson as chief health policy advisor, with

special emphasis on translational medicine including electronic systems (eHealth) and innovation, biosecurity, human subjects' protection, women's health, elder care and HIV/AIDS. During her tenure, federal adoption of eHealth communication standards was initiated, eHealth programs were begun in the Indian Health Service, and a response plan for pandemic influenza was drafted for the G8 health ministers. She resigned in 2003, and is currently serving as a Director of Vertex Pharmaceuticals, Cambridge, MA, Phase Forward, Waltham, MA, VaxGen, Brisbane, CA, and Theravance, South San Francisco, CA. She is a Commissioner of the Urban Indian Health Commission, and a member of the Scientific Advisory Committee for the Global Alliance for TB Drug Development.

In 2003, Dr. Slater was the Lloyd H. Smith Visiting Professor of Medicine at the University of California, San Francisco; she received the Virginia Kneeland Frantz '22 Distinguished Women in Medicine Award from the College of Physicians & Surgeons; and was selected to the national Library of Medicine's Exhibition "Changing the Face of Medicine: Celebrating America's Women Physicians."

An accomplished flutist, Dr. Slater has studied with many America's foremost flutists and appeared as flute soloist with Arthur Fiedler and the Boston Pops. She now serves on the Board of Visitors of the New England Conservatory of Music. She is the mother of two sons.

John A. Thomas, PhD was born and educated in the Midwest. He received his undergraduate degree at the University of Wisconsin and his M.A. and PhD degrees at the University of Iowa. He has held professorships in departments of pharmacology and toxicology in several medical schools including Iowa, Virginia and West Virginia. Professor Thomas has been the mentor for many doctoral students and has trained several post-doctorals. From 1973 to 1982 he served as Associate Dean of the School of Medicine at West Virginia University where his responsibilities included graduate programs and research. In 1982, Dr. Thomas moved into the health care industry where he became Vice President for Corporate Research at Baxter Healthcare. While in industry, he was involved in new drug development including recombinant DNA-derived therapeutic agents. Dr. Thomas served as Vice President at the University of Texas Health Science Center at San Antonio from 1988–1998. He is the author of over a dozen textbooks and research monographs and has published nearly 400 scientific articles in the area of endocrine pharmacology and reproductive toxicology. He is a member of numerous societies including the Endocrine Society, the Teratology Society, American Society for Pharmacology and Experimental Therapeutics, Society of Toxicology, and the American College of Toxicology. Professor Thomas serves on several editorial boards of biomedical journals and has been a member of the National Library of Medicine Literature Selection Technical Review Committee. Dr. Thomas served as a Specialty Editor for

Toxicology and Applied Pharmacology, and is on the Editorial Board of Food and Chemical Toxicology. He served as member on the Air Force Science Advisory Board. He has been a member of the Institute of Medicine/National Academy of Science Committee on Micronutrients, and is past-Chairman of the Expert Advisory Committee of the Canadian Network of Toxicology Centers. He is a member of the FDA Science Advisory Board. Recently, Dr. Thomas served as Chairman of the NTP/NIEHS, Center for Evaluation of Risk to Human Reproduction, Expert Panel on Ethylene and Propylene Glycol as well as being a member of the Expert Panel on soy infant formula and genistein. He is a Diplomate and Fellow in the Academy of Toxicological Sciences as well as a Fellow in the American College of Toxicology. He continues to serve on many scientific boards and committees in the chemical and pharmaceutical industry. He served as Vice President for the Texas Society for Biomedical Research, as a member of the Board of Trustees of the International Life Sciences Institute and on the Board of Directors of the Academy of Toxicological Sciences. Dr. Thomas is Past-President of the Academy of Toxicological Sciences. He was named the 1999 recipient of the Distinguished Service Award from the American College of Toxicology. Dr. Thomas is Past-President of the American College of Toxicology. He is the recipient of several national awards including the Merit Award from the Society of Toxicology, Certificate of Scientific Service (USE.P.A.), Distinguished Lecturer in Medical Sciences (A.M.A.), Distinguished Service Award from the Texas Society for Biomedical Research and holds Distinguished Alumni Awards from both the University of Wisconsin and the University of Iowa. Recently, he was awarded an FDA Commissioner's Special Citation. He is an elected foreign member and Fellow of the Russian Academy of Medical Sciences.

P. Roy Vagelos, MD, is Retired Chairman and CEO of Merck & Co., Inc. He received an AB in 1950 from the University of Pennsylvania and an MD in 1954 from Columbia University. Following a residency at the Massachusetts General Hospital, he joined the National Institute of Health where from 1956–1966 he served as Senior Surgeon and then Section Head of Comparative Biochemistry. In 1966 he became Chairman, Department of Biological Chemistry, Washington University School of Medicine in St. Louis and in 1973 founded the University's Division of Biology and Biomedical Sciences. He joined Merck Research Laboratories in 1975 where he was president until 1985 when he became CEO and later Chairman of the company. He retired in 1994.

Dr. Vagelos is a member of the National Academy of Sciences, the American Academy of Arts and Sciences, and the American Philosophical Society. He has received many awards in science and business as well as 14 honorary doctorates. In the past he was Chairman of the Board of the University of Pennsylvania, a member of The Business Council and The Business Roundtable, and served on the

boards of TRW, McDonnell Douglas, Estee Lauder and Prudential Finance. He also served as Co-Chairman of the New Jersey Performing Arts Center and President and CEO of the American School of Classical Studies in Athens.

He is currently Chairman of Regeneron Pharmaceuticals and Theravance, two biotech companies. He is also Chairman of the Board of Visitors at Columbia University Medical Center where he also chairs the Capital Campaign. He serves on a number of public policy and advisory boards, including the Donald Danforth Plant Science Center and the Danforth Foundation.

Catherine E. Woteki, PhD, RD is Global Director of Scientific Affairs for Mars, Incorporated, a multinational food, confectionery, and pet care company. She joined Mars, Inc. in August, 2005, and in this role manages the company's scientific and regulatory positions on matters of health, nutrition, and food safety.

Prior to joining Mars, Inc., Dr. Woteki held positions in academia and government. From 2002–2005, she was Dean of Agriculture and Professor of Human Nutrition at Iowa State University which is ranked among the world's top five research institutions in the food and agricultural sciences. From 1997–2001, she served as the first Under Secretary for Food Safety at the US Department of Agriculture overseeing the Food Safety and Inspection Service and the US government's Office for the Codex Alimentarius Commission, and coordinating US government food safety policy development and USDA's continuity of operations planning. She also worked for two years in the White House Office of Science and Technology Policy where she co-authored the Clinton Administration's science policy statement, "Science in the Public Interest" and as the Deputy Under Secretary for Research in the US Department of Agriculture.

Dr. Woteki is a nutritional epidemiologist, and her research interests include nutrition and food safety policy, risk assessment, and health survey design and analysis. She is the author of over 60 refereed scientific articles and 12 books and technical reports. During her tenure as Director of the Food and Nutrition Board, she had direct responsibility for 27 studies and she co-authored a nutrition book for the public entitled Eat for Life which became a Book of the Month Club selection.

Dr. Woteki is a registered dietitian and is active in several scientific organizations including the American Society for Nutrition, the Institute of Food Technologists, and the American Dietetic Association. She is a fellow of the American Association for the Advancement of Science and a member of the Institute of Medicine for which she was chair of the Food and Nutrition Board in 2003–2005. She has been honored with the American Dietetic Association's Lenna Frances Cooper Award, the

Public Health Service's Special Recognition Award, and the Elijah White Award of the National Center for Health Statistics.

Dr. Woteki has served on the Board of Trustees of the International Life Sciences Institute, the Board of Directors of the Federal Crop Insurance Corporation and the Board of Directors of the USDA Graduate School. She was leader of US government delegations to the International Congress on Plant Sciences and the FAO Consultation on Plant Genetic Resources in 1996, the OECD Ad Hoc Group on Biotechnology and Other Aspects of Food Safety in 2000, and the Codex Committee on General Principles also in 2000.

The State of Science at the Food and Drug Administration

By Peter Barton Hutt*

Introduction

Science at the Food and Drug Administration (FDA) today is in a precarious position. In terms of both personnel and the money to support them, the agency is barely hanging on by its fingertips. The accumulating unfunded statutory responsibilities imposed on FDA, the extraordinary advance of scientific discoveries, the complexity of the new products and claims submitted to FDA for pre-market review and approval, the emergence of challenging safety problems, and the globalization of the industries that FDA regulates -- coupled with chronic underfunding by Congress -- have conspired to place demands upon the scientific base of the agency that far exceed its capacity to respond. FDA has become a paradigmatic example of the "hollow government" syndrome -- an agency with expanded responsibilities, stagnant resources, and the consequent inability to implement or enforce its statutory mandates. For the reasons set forth in this report, Congress must commit to a two-year appropriations program to increase the FDA employees by 50 percent and to double the FDA funding, and then at least to maintain a fully burdened yearly cost-of-living increase of 5.8 percent across all segments of the agency. Without these resources the agency is powerless to improve its performance, will fall only further behind, and will be unable to meet either the mandates of Congress or the expectations of the American public.

Congress and the nation therefore have a choice. We can limp along with a badly crippled FDA and continue to take serious risks with the safety of our food and drug supply, or we can fix the agency and restore it to its former strength and stature. If Congress concludes to fix FDA, however, this cannot be done cheaply. It will be necessary to appropriate substantial personnel and funds to reverse the damage done to FDA in the past two decades.

There should be no doubt about the ability of FDA to absorb and put to good use a 50 percent increase in personnel and a 100 percent increase in funds over two years. Beginning in 1992, four of the FDA Centers have readily accommodated large increases in personnel and funds under user fee statutes and still have major neglected unfunded scientific responsibilities.

* This report was prepared as part of Mr. Hutt's service on the Science Review Subcommittee of the FDA Science Board and reflects his personal analysis and opinion on the matters considered by the Subcommittee. Mr. Hutt is a Senior Counsel at Covington & Burling LLP and teaches a course on Food and Drug law each year at Harvard Law School. He served as FDA Chief Counsel during 1971-1975.

Adequate resources -- both personnel and money -- alone will not be sufficient to repair the deteriorating state of science at FDA. Strong scientific leadership and a new vision to access applicable scientific knowledge and expertise from throughout the government and the private sector are essential to rebuilding the agency's ability to implement its scientific responsibilities effectively. While increasing the FDA staff and doubling the FDA's annual funding by itself will not achieve this objective, without adequate resources even the most creative leadership cannot hope to accomplish what must be done. In short, a substantial increase in resources is a necessary, but not sufficient, requirement to restore the science base at FDA to a level adequate to permit the agency to address its important public health mission.

This report first reviews the overall state of science at FDA in terms of the resources available to the agency as compared with the accumulating unfunded mandates imposed by Congress. It then considers the scientific personnel and resources needed in order to return FDA to a fully-functioning science-based agency in the future.

Lack of Historical Database

It must be emphasized at the outset that analyses of the FDA budget and regulatory activities over the past decades have been hindered, and in many instances have been made impossible, by the lack of a validated FDA historical database. A review of the state of science at FDA should proceed on the basis of well-documented and uniform historical data reflecting the entire spectrum of the agency's budget, personnel, and workload. Because of chronic underfunding of the agency, and the need to focus all available resources on FDA's important public health mission, the agency has never developed a consistent historical database on which adequate analyses can be undertaken. For example, under each of its four user fee statutes the funds and personnel are split among one or more Centers, the Field offices, and various FDA headquarters administrative offices, but FDA has no comprehensive compilation that breaks out these numbers by recipient. FDA's data for the years prior to 1997 do not separate the Centers from the Field force. The agency is unable to break out the personnel and funding levels for cosmetics from the numbers for the Center for Food Safety and Applied Nutrition (CFSAN). The numbers shown in Tables 4 and 5 are therefore a combination of publicly-available data and extrapolations, derived from a variety of sources. The Final Report of the Advisory Committee on the Food and Drug Administration to the Secretary of HHS (May 1991) found the same deficiencies 16 years ago (page 33). In spite of these substantial limitations, however, FDA worked hard to compile sufficient publicly available information to support the development of Tables 4 and 5.

For an agency that traces its origin to 1862 and that has had a federal statutory mandate to regulate the nation's food and drug supply since 1906, this lack of a historical database for budget, personnel, and

regulatory activities is appalling. FDA cannot be managed effectively without understanding where its funds and personnel are allocated as well as the historical trends for its regulatory responsibilities. A science-based approach to regulation requires an infrastructure that can produce adequate data to underpin regulatory planning that will most efficiently and effectively promote and safeguard the American food and drug supply. But it is also the fault of Congress, not just FDA, that such a database does not exist. Congress has failed to provide FDA with personnel and funds adequate to support the information technology and staff essential for such an effort.

Accumulating Unfunded FDA Statutory Mandates

When the Federal Food, Drug, and Cosmetic Act was originally enacted in 1938, the regulatory and compliance issues faced by FDA were comparatively simple and required far less reliance upon science. The issues of adulteration and misbranding could be handled by well-trained Field inspectors located throughout the country. The need for Ph.D.s and M.D.s was modest, and very few were employed by the agency.

There was only one exception. The 1938 Act included pre-market notification (but not pre-market approval) for the safety (but not the effectiveness) of human and animal new drugs. From that modest beginning, FDA's role as gatekeeper to new products has expanded enormously. Through the enactment of a series of landmark statutes beginning in the 1950s and extending through the 1970s, FDA was given a mandate by Congress to review and approve, prior to marketing, the safety of color additives, human food additives, and animal feed additives, and to review and approve the safety and effectiveness of human new drugs, animal new drugs, human biological products, and medical devices for human use. As a practical matter, today no new pharmaceutical product or medical technology can be marketed in the United States without FDA first determining that it is safe and effective for its intended use. In 1990, Congress added pre-market approval for disease prevention and nutrient descriptor claims for food products, and in 1994 it added pre-market review for new dietary supplement ingredients. These unprecedented new responsibilities forever transformed the nature and scope of the agency's workload.

As these and other statutory mandates accumulated, the need for adequately-trained FDA scientific personnel, and the resources appropriate to support them, increased exponentially. With the rapid advance of such scientific disciplines and techniques as analytical chemistry, food technology, recombinant DNA technology, quantitative risk assessment, modern engineering and electronics, the biological sciences, blood and tissue technology, genomics and the other "omics," and nanotechnology -- to name just a few -- FDA has struggled to recruit well-trained scientists and to keep up with new scientific developments in order to maintain a solid medical and

scientific basis for its pre-market review and approval decisions. Without congressional appropriations for increased scientific personnel and funds to support participation in professional scientific meetings and to maintain cutting-edge educational programs within the agency, FDA staff become increasingly isolated and fall behind their counterparts in academia and the regulated industry.

FDA encounters tremendous problems in implementing the burgeoning number of new statutory responsibilities imposed by Congress each year. Table 1 lists the more than 100 statutes that directly impact FDA enacted by Congress only since 1988 -- an average of more than 6 each year. These are in addition to the core provisions of the 1938 Act itself and another 90-plus statutes directly involving FDA that were enacted during 1939-1987. Each of these statutes requires some type of FDA action. Many require the development of implementing regulations, guidance, or other types of policy, and some require the establishment of entire new regulatory programs. Virtually all require some type of scientific knowledge or expertise for the agency adequately to address them. Yet none of these statutes is accompanied by an appropriation of new personnel and increased funding designed to allow adequate implementation. In the history of our country, no other Federal regulatory agency has ever faced such an onslaught of new statutory mandates without appropriate funding and personnel to implement them. Instead, the agency is expected to implement all of these new unfunded congressional mandates with resources that, in the corresponding time, represent at best a flat budget. Not surprisingly, many of the new congressional mandates languish for years or cannot be implemented at all.

For example, in 1994 Congress authorized FDA to establish good manufacturing practice (GMP) regulations for dietary supplements. It took nine years before FDA published proposed regulations in 2003, and four years later the final regulations have just now finally been promulgated. In 1997, Congress required drug manufacturers to notify FDA about the discontinuance of specified drug products. FDA proposed regulations to implement this requirement in 2000, and seven years later has just now promulgated the final regulations.

As another example, it is well-documented that contamination of railroad cars used to transport food and other FDA-regulated products can result in serious health hazards. Congress sought to address this in 1990 by authorizing the Department of Transportation to issue regulations to prevent the contamination of these important products, but DOT eventually determined in 2004 that the expertise for assuring their safety lies with FDA. Congress then enacted a new law in 2005 requiring FDA to establish regulations to assure that food is not transported under conditions that may render the food adulterated. No new personnel or money accompanied this statutory requirement. Substantial scientific resources will be needed if the agency is expected to develop and implement appropriate regulations. As of today, FDA has taken no action to develop these regulations, and has no plans to

do so, because it does not have the requisite scientific resources. This matter is not even mentioned in the 2007 list of the top 150 priorities for CFSAN.

These simple examples illustrate the problems that FDA encounters with the enactment of every one of the new statutory responsibilities embodied in the legislation listed in Table 1. Because they are unfunded mandates, they are often unimplemented mandates.

Just a short while ago, Congress once again enacted an unfunded FDA omnibus statute, the Food and Drug Administration Amendments Act of 2007, that demands substantial FDA scientific resources to analyze and implement. It consists of 11 separate titles, each of which is a comprehensive statute in and of itself, for a total of 155 pages of new regulatory responsibilities -- with no plans for additional appropriated funds or personnel to implement it. Parts of it are funded by user fees, but large parts are not. There are no personnel or funds in the proposed FDA 2008 appropriations to implement the major new programs this new statute mandates. FDA cannot manage this process by tired old slogans like "work smarter." These only insult an already overworked and very dedicated agency staff. The statutes documented in Table 1 -- and particularly the FDA Amendments Act of 2007 -- can only be implemented by diverting the agency's staff from one task to another. To meet the requirements of a new statute, in short, FDA must abandon work on an old one. That is exactly what has been happening at FDA for the past 20 years. The only way to stop the disintegration of FDA's core responsibilities and still maintain the ability to accept new mandated programs is for Congress to appropriate the personnel and funds needed to do both.

Just the congressional consideration of these new statutes through House and Senate legislative hearings -- and the related investigational hearings and letters by other committees and individual members of Congress -- siphon off substantial time of FDA scientists whose expertise is needed to assure that the agency responds fully and accurately. This is unquestionably an important part of our democratic process. But it is also an unfunded major activity that is not accounted for in the budget process even though it consumes thousands of hours of FDA personnel.

In addition to the laws listed in Table 1, which directly require FDA to take action, Congress has enacted a number of statutes of general applicability that place a large administrative burden on FDA in conducting its daily work. Representative statutes of general applicability that require substantial FDA resources for compliance are listed in Table 2. For example, in order to promulgate a regulation, FDA must at a minimum include, in the preamble, not only full consideration of all the substantive issues raised by the regulation itself, but also a cost-benefit analysis, an environmental impact discussion, a federalism evaluation, a small business impact statement, a determination whether there is an unfunded mandate

impact on state or local governments, and an analysis of paperwork obligations. The proposed and final regulations must be reviewed and approved by the Department of Health and Human Services (DHHS) and the White House Office of Management and Budget (OMB). However well-intentioned, these responsibilities place a major burden on FDA and require that scientific resources be diverted from other areas in order to assure compliance. This has led FDA to avoid rulemaking wherever possible and to substitute informal guidance or to take no action whatever on important regulatory matters.

The impact on FDA of just one of these statutes of general applicability can be readily quantified. The Freedom of Information Act requires FDA, along with other federal agencies, to provide documents in the agency's files to the public upon request. This is unquestionably a statute of major importance to the country. Because FDA is the repository of substantial information that is of interest to the regulated industry, academia, and the general public, FDA receives each year more FOI requests than any other government agency except the Federal Bureau of Investigation. Handling these requests places a substantial burden on FDA personnel and funds. To alleviate the cost to FDA, Congress included in the FDA Revitalization Act of 1990 authorization to establish a revolving fund to pay for FOI costs. This has, however, produced only a modest offset to the agency FOI costs. In 2006, FDA received a total of \$493,202 in FOI fees, compared to the overall agency FOI costs of more than \$11 million. In many instances, it is the scientists and not the support personnel at FDA who must respond to these FOI requests, in order to assure that the correct documents are being provided and that confidential information is not made public. These are the same scientific personnel who have, as their major priority, the review and approval of applications for new products and claims.

The FOI Act requires that FDA determine within 20 days whether it will provide the requested documents, and provide the documents "promptly" thereafter. Because of its lack of funds and personnel, FDA reduced its FOI staff from 123 in 1995 to 88 in 2006. As a result, its backlog of unfilled FOI requests has grown from 13,626 in 2000 to 20,365 in 2007. Some requests date back four years and even longer. The entire system is clearly broken. It cannot be fixed by admonitions that the agency should "do better." It can only be fixed by congressional appropriation of adequate resources devoted to implementing the FOI Act and providing this information to the public.

The statutes of general applicability are not the only directives that have a strong impact on FDA. Every President in the past 40 years has issued one or more Executive Orders that impose additional obligations on FDA. A representative sample is set forth in Table 3. These Executive Orders have the same binding status as a statute and can have as great or greater impact.

For example, President Bush recently issued an Executive Order delegating review of administrative agency guidance to OMB. As noted above, FDA began to issue guidance in the 1970s in order to provide useful information to the regulated industry on important regulatory policy issues, without the formality of promulgating regulations. Now the agency scientists must devote substantial time to determining which guidance fall under OMB review. For each guidance that requires OMB review, the agency must decide whether it has the resources to pursue the matter at all and, if so, what other matters must be abandoned in order to carry this one forward. This is not a criticism of this Executive Order. But Congress must realize that it entails substantial administrative burdens that require additional personnel and funds to implement.

The combined weight of these unfunded FDA statutes, statutes of general applicability, and Executive Orders is tremendous. Each includes additional responsibilities for the agency without commensurate appropriations for personnel and funds. The result is that, with relatively flat funding and a very large increase in what the country expects from the agency, FDA is falling further and further behind.

These unfunded mandates cascade down on FDA from all sides of the political spectrum. It is not a problem caused by partisan politics. The Administrations of President Clinton and President Bush have been equally unresponsive to FDA’s needs. Nor does this report question the justification for these mandates. Rather, it is the undeniable fact that these mandates are unfunded, and thus that FDA lacks the capacity to implement them, that is objectionable. The country cannot withhold the requisite scientific resources from FDA and then complain that the agency is incapable of meeting our expectations.

This disparity between expectations and resources has become increasingly apparent to the public in the past five years. Daily media headlines have focused on safety problems with prescription drugs, medical devices, the food supply, and now pet food as well. Without adequate appropriations, this will not just continue but increase.

The result of this very visible deterioration in FDA resources is a sharp decline in public confidence. Three decades ago, FDA ranked among the most respected federal agencies, with a public confidence rating of about 80 percent. Today, it has plummeted to between 30 and 40 percent:

FDA Public Confidence Rating (Harris Poll)	
1970s	80%
2000	61%
2004	56%
2006	36%

As long as appropriations lag behind public expectations and new responsibilities imposed by Congress, this decline in public confidence can be expected to continue.

At the heart of the problem is the lack of adequate scientific personnel and resources. As noted above, prior to 1970 FDA was primarily a law enforcement agency. Beginning in the 1970s, however, FDA became a modern science-based regulatory agency. With the advent of pre-market review and approval requirements for FDA-regulated products, the bulk of FDA work shifted from the courts to administrative decisions made within the agency. These administrative decisions are almost always based upon science.

The reaction of Congress to the decline of FDA has been to enact further legislation, not to appropriate additional resources. This vastly misperceives the problem. The current reduced state of FDA is not the result of a lack of statutory authority and mandates to foster and protect the public health. It is the direct result of the lack of adequate appropriations of personnel and money to do the job. More statutes only exacerbate the problem.

Scientific research agencies like NIH and CDC have had substantial increases in appropriations over the past two decades but FDA has not. Since 1988, NIH appropriations have increased \$22.264 billion and CDC \$5.261 billion as compared to \$1.096 billion for FDA. The regulated industry has strongly supported higher FDA appropriations, but to no avail. Whatever the reason for this disparity, it is now time for Congress to make up the difference. Today, NIH and the pharmaceutical industry are investing more than \$60 billion annually in the search for new lifesaving pharmaceutical products. The important medical and scientific discoveries that flow from our country's preeminent research laboratories will be severely hindered from reaching the patient's bedside unless FDA is given adequate resources.

Need to Leverage Other Scientific Sources

FDA is a science-based regulatory agency, not a scientific research organization. Basic scientific research should be conducted at the National Institutes of Health (NIH), in academia, and in other basic science organizations, not at FDA. But it is vital that FDA have access to that research in order to apply it to the daily regulatory decisions with which it is charged. FDA cannot make well-reasoned decisions on the marketing of new medical technology if it does not have within the agency up-to-date expertise on the science that underpins that technology.

There are also some areas of applied science that are vital to FDA's regulatory mission, such as the development and validation of analytical methods. This form of regulatory science must continue to be supported within the agency.

FDA must take advantage of the programs in other federal agencies that complement the FDA mission and that can, with effective coordination, multiply the impact of what FDA can do alone. For example, there are food safety programs in the Centers for Disease Control and Prevention, the United States Department of Agriculture, State agencies, and the land grant universities. Yet FDA has inadequate appropriations to leverage these resources through a closely-cooperating consortium that could greatly enhance the effectiveness of all the participants.

With increasing technical specialization, FDA must focus on the core areas of scientific expertise that must reside within the agency in order to permit FDA to continue its historic mission, and those areas that can more appropriately be outsourced in order to access technical expertise. No better example of outsourcing exists than information technology. FDA cannot recruit sufficient technicians to allow the agency to design and build a state-of-the-art information technology system by itself, nor should it try to do so. But FDA still needs a core information technology staff to manage the contractors and coordinate the entire effort. To accomplish this for the entire agency will require major new appropriations.

One of the most important issues facing FDA today is the development of a modern active post-market safety surveillance network for drugs, biological products, and medical devices that will establish an early warning system by electronically linking public and private adverse event databases throughout our healthcare system. FDA has struggled with this issue for four decades, lacking both the technology and the appropriations to build an appropriate system. With the advent of current cutting-edge information technology, the technology part of the issue can now readily be addressed. But without substantial immediate appropriations FDA still cannot move forward with a program that is vitally needed to assess the continued safety of our medical products once they reach the marketplace. Congress must recognize this need and act on it promptly, or sit by and witness continuing media revelations of product safety problems.

Because congressional appropriations have failed to support the science base at FDA at an adequate level, in desperation FDA and the regulated industries have sought to fill the gap with user fees -- first for human prescription drugs and biological products, and more recently for medical devices and animal drugs. Even with these non-appropriation funding mechanisms, however, FDA has failed to keep pace with the mandates of Congress and the expectations of the public. Regulatory decisions must therefore be made by an agency that has inadequate scientific personnel and resources. It is not the fault of FDA leadership that this has occurred. It is the fault of the entire country that our most important health agency has been neglected to the extent that the science base on which virtually all of its decisions depend has substantially deteriorated. Unless something is done about it immediately, the ability of FDA to pursue its public

health mission -- to promote and protect the health of the American people -- will become even more tenuous.

Unfinished FDA Safety Programs

The lack of adequate scientific personnel and the resources to support them has had a major adverse impact on important FDA regulatory programs to assure the continued safety of marketed products. For example, on several occasions FDA has established comprehensive reviews of products after they have been marketed, either at the direction of Congress or on its own initiative. Virtually all of these reviews remain unfinished for lack of agency resources.

Color Additives. At the direction of Congress, in 1960 FDA began a review of the safety of all color additives used in food, drugs, and cosmetics since 1906. Today, 47 years later, the lakes of all color additives used in these products still have not yet been the subject of a final safety decision by FDA even though they have been used in marketed products for the past 100 years.

Prescription Drugs. The Drug Amendments of 1962 directed FDA to review the effectiveness of all drugs for which an NDA had become effective solely on the basis of safety between 1938 and 1962. This was implemented by the Drug Efficacy Study Implementation (DESI) program. Today, 45 years later, approximately 20 of these DESI drugs still remain on the market without a final determination of effectiveness.

Nonprescription Drugs. In 1972, FDA established the OTC Drug Review, to review the safety, effectiveness, and labeling of all nonprescription drugs then being marketed. Today, 35 years later, there remain several categories of OTC drugs, representing thousands of separate products, that have not yet been the subject of a final determination under the OTC Drug Review.

Biological Products. Following the transfer of responsibility for the licensing of biological products from NIH to FDA, in 1973 the agency announced that it would conduct a review of the safety, effectiveness, and labeling of all biological products marketed pursuant to licenses issued from 1902 to 1972. Today, 34 years later, the Biologics Review remains only partially completed.

Food Ingredient GRAS List Review. In 1969, President Nixon directed FDA to undertake a comprehensive review of the safety of all food ingredients listed by the agency as generally recognized as safe (GRAS) and thus as marketed without the need for FDA review and approval of safety through promulgation of a food additive regulation. After completing part of the GRAS List Review, FDA abandoned this program for lack of resources and now reviews the safety of marketed GRAS food substances only when specific issues are raised.

Human Food Ingredient GRAS Affirmation. In 1972, FDA established a procedure under which food ingredient manufacturers who marketed their products as GRAS could obtain affirmation from FDA of the safety of these ingredients. Because of a lack of resources FDA abandoned this procedure in 1997 and substituted for it a simple notification procedure under which the agency issues letters stating that the agency has “no questions” but makes no affirmative determination of safety. Today, ten years later, the proposed regulation for this new policy has not yet been promulgated in final form even though the new policy has been fully implemented for human food ingredients.

Animal Feed Ingredient GRAS Affirmation. The 1997 proposed GRAS notification procedure applied to animal feed ingredients as well as human food ingredients. Because of a lack of resources, the Center for Veterinary Medicine (CVM) not only abandoned the GRAS affirmation procedure but declined to implement the new GRAS notification process as well. On request, CVM issues letters stating that the agency has “no objections” but makes no affirmative determination of safety. On the basis of these letters the regulated industry then handles all feed ingredient GRAS issues through the Association of American Feed Control Officials (AAFCO) and individual State agencies.

Review of Pre-1976 Class III Medical Devices. Under the Medical Device Amendments of 1976, all pre-1976 medical devices that are classified by FDA as requiring pre-market approval for safety and effectiveness (Class III) are required to be the subject of a regulation promulgated by the agency either calling for the submission of a pre-market approval (PMA) application or reclassifying the device. Today, 31 years later, up to 15 of these categories of pre-1976 devices -- including post-1976 devices determined to be substantially equivalent -- remain on the market under Class III without an FDA review and decision on their safety and effectiveness.

Food Additive Regulations. In 1977, FDA announced that it would undertake a cyclic review of all food additive regulations to assure that past food safety decisions remained currently justified. Because of a lack of resources FDA abandoned this program in the early 1980s and now reviews the safety of marketed food additives only when specific issues are raised.

Unapproved New Drugs. The DESI program required by the Drug Amendments of 1962, for new drugs that were covered by an NDA between 1938 and 1962, did not extend to drugs that had been marketed without an NDA on the basis of an independent determination by the manufacturer that they were GRAS and thus exempt from the requirement for an NDA. After one of these unapproved new drugs caused serious adverse events that required a nationwide recall, FDA committed to Congress in 1984 that it would review the safety and effectiveness of these products

and take appropriate action. Because FDA has taken action against fewer than ten of these types of drugs since 1984, thousands of unapproved drugs are now being marketed without any type of FDA review of safety or effectiveness and are estimated to represent approximately two percent of all prescriptions.

These represent only a few examples of numerous FDA programs that languish for lack of adequate scientific personnel and funding. They illustrate the problems that the agency faces when congressional appropriations are inadequate to permit FDA to devote scarce resources to important product safety programs.

Lack of Adequate FDA Appropriations

No one outside FDA has enough information about the agency to conduct a zero-based budget analysis for FDA. It is likely that FDA itself has numerous materials that would bear upon such an analysis, but the agency states that it is not able to make those public.

This report therefore pursues a different approach. Attached are tables that present a partial statistical history of the congressional appropriations for FDA personnel and funds for the past 20 years, compiled from publicly-available sources. Tables 4 and 5 cover the 20-year period of 1988 - 2007 (or, where these figures are not available, the most recent years for which they are available). As the last column in Table 5 shows, from 1988 to 1994 FDA's appropriated personnel and funding kept even with its increasing responsibilities and exceeded inflation. The agency's appropriated personnel increased from 7,039 to 9,167 (a gain of 2,128 people) and its funding from \$477.504 million to \$875.968 million (a gain of \$398.464 million). In 1994, however, FDA hit a brick wall. From 1994 to 2007 the agency's appropriated personnel decreased from 9,167 to 7,856 (a loss of 1,311 people), returning it almost to the same level that was appropriated 20 years earlier. FDA's appropriated funding during this time increased by \$698.187 million, but this was only about two-thirds the funding needed to keep up with FDA's fully burdened cost-of-living increase of 5.8 percent, compounded yearly. Thus, over the entire 20 years FDA gained only 817 employees -- an increase of 12 percent -- and lost more than \$300 million to inflation, while faced with implementing the new statutes listed in Table 1 and the agency's substantial other core responsibilities under the 1938 Act. Confronted with a burgeoning industry as documented in Table 6, it became increasingly impossible for FDA to maintain its historic public health mission.

This report concludes that a substantial increase in appropriations is essential to halt the disintegration of FDA and to allow the agency to regain its former strength and vitality. A 50 percent increase in personnel (FTE) and a 100 percent increase in funds, over a two-year period, is necessary in order to rescue FDA from its current precarious condition.

The FDA appropriations for 2007 provide for 7,856 employees. The recommendation of this report would raise this appropriated level to 9,820 employees in 2008 -- just slightly more than the 9,352 employed by the agency in 1994. The appropriated number of employees would then rise to 11,794 in the following year. This represents only a 64 percent increase from the 7,210 employees appropriated for FDA in 1988, 20 years earlier. Considering just the enormous workload created by the new 100-plus statutes enacted by Congress during this time, this increase is quite modest.

Doubling the funds appropriated for FDA is essential to rebuild regulatory programs that have been decimated over the past 20 years. The recommendation of this report would raise the appropriated funds for FDA from \$1.574 billion today to \$2.361 billion in 2008 and to \$3.148 billion in the following year. Applying FDA's fully burdened cost-of-living factor for the agency of 5.8 percent, compounded annually, for the past 20 years means that \$1.475 billion in FDA funding is required just to restore the agency to the same level today as in 1988 (\$477.504 million), without consideration of the additional burdens imposed on the agency under the new statutes listed in Table 1. But we need to do much more than just that. For example, substantial funds are needed to construct a nationwide adverse event warning system for medical products and new inspection programs for both domestic and imported products, just three current high priority new programs for the agency. Together just these programs will cost well over \$500 million to plan, implement, and maintain. These new funds are vitally needed to make up for years of neglect. The cumulative gap between the funds FDA has needed all these years, and the amount actually appropriated, far exceeds the funding this report is recommending. This recommendation will be sufficient, however, to lift the agency from its present state of disrepair and to allow the rebuilding process to begin.

It must be emphasized that this is not a one-time quick fix. Appropriations for FDA personnel and funding must have indexed increases each year, to prevent another sustained period of deterioration.

The 3,928 new employees that will be hired, and the \$1.574 billion in new funds, over this two-year period should primarily be allocated to functions not presently supported by user fees. As discussed in greater detail below, user fees have completely distorted the current FDA budget. The applications review functions for human drugs, biological products, medical devices, and animal drugs have been supported by both indexed appropriations and user fees, while the rest of FDA has stagnated. Accordingly, most of the increased appropriations that we recommend should be allocated to the functions of FDA that have not been supported by user fees, such as CFSAN and the Field force.

FDA regulates an estimated 25 percent of each individual's personal consumption in our country. Each citizen presently pays only \$5.21 per year -- about 1.5 pennies per day -- to support the agency. Our proposal would raise this to \$10.42 per year, or 3 cents per day. Considering that the products that FDA regulates are essential to sustain life itself, this is a bargain.

Destructive Impact of User Fees

FDA and industry have resorted to user fees to prop up the agency since 1992 only because the pre-market review and approval functions of the agency would collapse without them. In the long run, however, funding FDA by a tax on the regulated industry is not an appropriate solution to the agency's needs and should be abandoned. This approach has clearly contributed to the decline in FDA's public credibility. This report agrees with the Institute of Medicine that Congress should return to providing personnel and funds to FDA by appropriations, not by user fees.

The advent of user fees for prescription drugs and biologics has, in fact, shielded the serious deterioration of FDA science from public view. In 2007 the agency obtained \$352 million and 1,519 staff through user fees for new drugs and biological products. But these new resources are specifically limited to the review process for new drug applications (NDAs) and biological license applications (BLAs) and to related safety functions. For example, they do not support the review and promulgation of OTC drug monographs; or the review and decisions relating to DESI and non-DESI unapproved new drugs; or the Critical Path initiative; or post-market compliance review of product labeling and advertising; or the regulation of generic drugs; or Field post-market compliance action to assure the enforcement of FDA GMP requirements; or action relating to counterfeit or illegal internet and imported drugs; or numerous other activities that make important contributions to FDA regulation of pharmaceutical products. Because user fees have focused narrowly on the NDA/BLA review function and the user fee statutes require an annual cost-of-living increase for this function only, the appropriations for the rest of the regulatory process for drugs and biological products have stagnated. Thus, CDER and CBER today are divided into two parts -- the rich (supported by both indexed appropriations and user fees) and the poor (supported by flat or reduced appropriations). This intolerable disparity fails to recognize the importance of all of the parts of these Centers that contribute to the regulation of drugs and biological products.

A close analysis of how user fees actually work reveals an even more pernicious impact on the rest of the FDA budget. Each of the user fee statutes requires that Congress maintain its normal appropriations for the same function, indexed for inflation. At first blush, this makes sense. User fees are intended to add to congressional appropriations, not to replace them. Thus, funding and personnel for the functions of pre-market review and approval of new drugs, biological products,

medical devices, and new animal drugs receive a guaranteed cost-of-living increase each year as well as the user fees. But the impact on FDA as an institution is highly destructive. This system not only creates rich and poor functions within the four Centers that have user fees, but it leaves the remaining two Centers, CFSAN and NCTR, and the FDA Field force absolutely destitute.

This can be illustrated using the FDA budget figures for 2002 and 2005. FDA’s total program funding (including user fees) was \$1.37 billion in 2002 and \$1.62 billion in 2005, broken down in pertinent part as follows:

Total FDA Program Funding (\$ Millions)		
	2002	2005
Total FDA Program	1,370.000	1,620.000
Total Review Functions	344.930	637.551
User Fees	181.553	305.288
User Fee Indexing	163.377	332.263
Total Core Functions	854.185	604.035

As a result of user fees the review functions increased substantially, at the expense of the Agency’s core functions:

Percent of Total FDA Program Funding		
	2002	2005
Review Functions	25%	39%
Core Functions	62%	37%

In these three years alone, the core functions of FDA -- all of its basic responsibilities for implementing the 1938 Act and its hundreds of amendments -- lost \$250 million in funding, an incredible reduction of 29 percent. The core functions dropped precipitously from 62 percent to 37 percent of the total FDA program funding. And since 2005, it has only become worse. This is the real impact of user fees. It documents the systematic dismantling of the FDA’s core mission.

Lack of Adequate FDA Personnel

Nor is money alone the answer to the current crisis in FDA science. FDA needs a major increase in scientific personnel and support staff if it is to regain its former strength and stature. Indeed, FDA’s most serious deficit during the past 20 years has been the steady erosion in its human capital. Table 5 shows that the total appropriated personnel level in 1988 was 7,039. Today, 20 years later, the appropriated FTE level is 7,856, an increase of only 817 positions, or 12 percent -- and a

loss of 1,311 positions, or 14 percent, since 1994. The avalanche of laws documented in Table 1, together with the increase shown in Table 6 in the FDA-regulated industry, justify the attention of a substantial increase in the agency’s scientific personnel.

One example will illustrate this problem. Each year FDA receives an increasing number of reports of adverse events associated with prescription drugs that are submitted by health care practitioners through MedWatch or by the NDA or BLA holder as expedited (for adverse events that are both serious and unexpected) or periodic (quarterly, annually, or at FDA’s request):

Total Adverse Event Reports Submitted to FDA			
1996	191,865	2002	322,691
1997	212,978	2003	370,898
1998	247,607	2004	423,031
1999	278,266	2005	464,068
2000	266,978	2006	471,679
2001	285,107		

Even with the 146 percent increase in these reports from 1996 to 2006, FDA has had no increase in personnel to review and evaluate these reports. Simple mathematics shows that in 2006 FDA reviewers spent 40 percent of the time on each report that they spent in 1996. Higher appropriations would not have changed this result. Only a greater number of scientific personnel can return FDA to a more adequate handling of product safety evaluations.

The same scientific deficit occurred with the submission of medical device reports (MDRs) to the Center for Devices and Radiological Health (CDRH). CDRH received 184,222 MDRs in 2005 and 325,742 MDRs in 2006 -- a 77 percent increase in only one year, with no increase in scientific personnel to review and evaluate them.

Science-trained personnel are also essential to audit the conduct of clinical trials submitted to FDA to support applications for FDA-regulated products and claims that require pre-market notification or pre-market approval -- such widely divergent products as artificial sweeteners, automatic defibrillators, new dietary supplement ingredients, blood products, and cancer and AIDS drugs. This biomedical monitoring function of FDA serves the dual purposes of protecting human subjects and verifying the validity of the clinical trial results. Because of its budget constraints, FDA currently conducts only a partial audit of about 1 percent of these trials.

It is a tragedy that, when Congress, other government agencies, and the press uncover deficiencies in FDA regulation, they blame the agency for the problem, not the actual root cause of the agency’s

inaction -- the failure of Congress to provide adequate funding and staff to handle the matter. For example, the HHS Inspector General's recent report excoriating FDA for inadequate monitoring of clinical trials drew a headline on the front page of the New York Times that read "Report Assails F.D.A. Oversight of Clinical Trials." Neither the Inspector General nor the New York Times sought to trace the problem to its source and thus to place the blame on Congress, where it really belongs. Every report urging greater FDA action on a particular program should be required to specify what program the agency should discard in order to take on the new one.

Training and mentoring FDA scientific personnel -- both within the agency and through independent professional and academic programs here and abroad -- is an acute need. Application reviewers throughout the agency run the risk of inconsistent or uninformed decisions absent continuing education, coordination, and collaboration. For example, Bayesian statistical techniques are encouraged at CDRH but discouraged at CDER. FDA needs a strategic and sustained program of agency-wide in-depth intellectual engagement with its reviewers, not to satisfy idle curiosity but to equip them with the knowledge to confront current issues in health and disease as they are presented in the applications submitted to the agency. Although the explosion of scientific knowledge over the past 20 years seems daunting enough, it promises to be even more overwhelming in the next 20 years. FDA must prepare for it. Without the personnel and funds to develop and implement such a program FDA reviewers and their decisions will be poorly informed and the public health will be poorly served.

Attracting and retaining qualified scientists is a serious problem at FDA. The regulated industry almost always offers higher pay and benefits than FDA for entry level personnel. And once FDA trains its scientists, their expertise in FDA regulatory practice and policy makes them even more valuable to the industry. Confronted with frustration from the working conditions at FDA -- too few personnel and too little money -- and the opportunity for higher pay and better working conditions in industry, it is not surprising that FDA's attrition rates for scientists are higher than in other federal scientific agencies. This can be addressed by FDA only through congressional appropriations of additional personnel and funds.

The type of project planning undertaken by scientific research organizations cannot be rigorously implemented by FDA. In addition to its routine regulatory responsibilities, FDA is a crisis management organization. At any moment, FDA scientists both in Washington and in the Field must be prepared to ignore their established priorities and statutory deadlines in order to confront safety issues raised by food contaminated with pathogens, animal feed and pet food with chemical contaminants, fish with antibiotics, malfunctioning medical devices, serious adverse events associated with prescription drugs, BSE in cattle, and a host of other problems for which the agency is responsible. Because these issues are broadcast instantly throughout

the country through the electronic media, Congress and the public expect immediate answers and action from FDA. It is essential that the agency always have a critical mass of scientific expertise adequate to respond knowledgeably and effectively. It is also essential for the country to understand that there are some questions for which there are no quick and easy answers and that this is no reflection on the dedication or ability of the FDA scientists. But to handle these communication crises, FDA has an inadequate staff throughout the agency.

Disintegration of CFSAN

The science functions within the FDA Center for Food Safety and Applied Nutrition (CFSAN) have been hit particularly hard. In the 15 years from 1992 to 2007, CFSAN suffered a reduction in force of 138 people, from 950 to 812, or 15 percent of its staff. During the same period, Table 1 shows that Congress enacted new legislation creating large new responsibilities for CFSAN, all of which required substantial scientific expertise for implementation. CFSAN has been expected to implement such complex statutes as the Nutrition Labeling and Education Act of 1990, the Dietary Supplement Health and Education Act of 1994, the FDA Modernization Act of 1997, the Food Safety and Security Amendments of 2002, the Food Allergen Labeling and Consumer Protection Act of 2004, and the Sanitary Food Transportation Act of 2005, and most recently the Dietary Supplement Adverse Event Reporting Act of 2006 and the Food Safety Amendments of 2007 -- to name just the most important unfunded food statutes enacted during this period -- while facing a loss of 138 people.

This disintegration of the FDA food regulation function has continued unabated over the past quarter century. Sixteen years ago the Final Report of the Advisory Committee on the Food and Drug Administration to the Secretary of HHS (May 1991) identified the same problems (Appendix D, page 1):

There are deep concerns about the viability of the foods program and the lack of agency priority for food issues. Decline in resources and program initiatives during the past 10-15 years indicate a lack of agency management attention and interest in this area, although public interest in, and concern for, an effective food program remain high.

The status of CFSAN today is far worse than it was in 1991.

Dietary supplements receive far too little attention within CFSAN, because of the lack of adequate funding for scientific personnel. Following the enactment of the Dietary Supplement Health and Education Act of 1994, the dietary supplement industry has experienced a major increase in sales. From 1990 to 2005, the annual sales of dietary supplements increased from \$5 billion to over \$20 billion. Because the manufacturers of these products are authorized by law to petition FDA for approval of disease prevention claims, and

to make claims relating to the impact of their products on the structure or function of the human body without requesting FDA approval, it is essential that CFSAN employ physicians and scientists who can monitor these claims and recommend regulatory action where the claims are not justified. But during the time that these claims were becoming more prevalent and prominent following enactment of the Nutrition Labeling and Education Act of 1990 and the Dietary Supplement Health and Education Act of 1994, and the landmark First Amendment case of Pearson v. Shalala in 1999, Congress reduced the personnel responsible for reviewing and regulating these claims by 145 people. It is impossible for CFSAN to fulfill its statutory obligations under these conditions. The scientific personnel at CFSAN cannot “do more with less.” They can only do less with less, and that is in fact what has happened.

Within CFSAN, the Office of Cosmetics has suffered even more than CFSAN itself. At one time, the cosmetic regulation function within CFSAN was funded adequately and had a robust regulatory program. These were the appropriations during 1972 - 1977 for the regulation of cosmetics:

Appropriations for Regulation of Cosmetics (\$ Millions)	
1972	\$1.308
1973	\$1.991
1974	\$2.425
1975	\$2.286
1976	\$2.581
1977	\$2.790

Approximately 60 FTE were engaged in the regulation of cosmetics at CFSAN during this period. By 1980, however, the appropriations were reduced to \$1.855 million and CFSAN had 39 personnel devoted to cosmetics. In 1997, this was reduced to 26 personnel. In 2007, there are only 14 staff employed at CFSAN to regulate cosmetics, supported by a minimal \$3.5 million in funding.

FDA has long stated that cosmetics are the safest products that the agency regulates. Nonetheless, there are important regulatory issues relating to cosmetics that deserve adequate attention by FDA. A total of 14 staff personnel is clearly insufficient for a credible regulatory program for cosmetics, an industry with more than \$60 billion in annual sales. Just to keep up with inflation since 1977, the appropriations for cosmetics must be at least \$10 million in 2007, instead of the \$3.5 it has received, and the personnel level must be restored accordingly

Deterioration of the FDA Field Force

The review and approval of product applications is not the only FDA function that requires scientific knowledge and training. FDA inspectors in the Field force -- in both domestic and foreign manufacturing establishments and at our ports of entry -- must daily make scientific evaluations of the FDA-regulated products that they encounter. In the past 35 years, however, the decrease in FDA funding for inspection of our food and drug supply has forced FDA to impose a major reduction in the number of inspections. For example, the following table documents the decline in Field inspections of food establishments:

FDA Inspection of Foreign and Domestic Food Establishments			
1973	34,919	1995	5,741
1975	22,471	2000	7,204
1980	29,355	2005	9,038
1985	12,850	2006	7,783
1990	7,077		

This represents a 78 percent reduction in food inspections, at a time when Table 6 documents that the food industry has been rapidly expanding. FDA conducted twice the number of foreign and domestic food establishment inspections in 1973 (34,919) than it did for all FDA-regulated products in 2006 (17,641). This is what happens when Congress fails to authorize sufficient personnel and appropriations for FDA adequately to implement the agency’s core statutory mandates.

The reduction in FDA establishment inspections has hit hardest at food and cosmetics. The law requires that FDA inspect every drug and medical device establishment in the United States at least once every two years. Although FDA repeatedly violates this unfunded statutory mandate, the agency does inspect drug and medical device manufacturers more frequently than food and cosmetic manufacturers. FDA estimates that the Field inspects food manufacturers at most once every ten years and cosmetic manufacturers less frequently. The agency conducts no inspections of retail food establishments and only limited inspections of food-producing farms, except in emergencies.

As a result of its lack of resources, the agency has recently announced that it will rely more upon State food and drug inspectors to fill the void. Because of similar budget constraints at the State level, however, and the variable number of inspectors in the individual States, this policy will produce useful assistance only in a few large States and is not an adequate substitute for regular FDA inspections throughout the country. For that reason, FDA Field officials recently truthfully and accurately testified before Congress that the agency is failing to meet its statutory obligations and is doing a poor job in

implementing the current law. They are to be commended for their candor and honesty.

At the same time, importation of food into the United States has been exploding. During 1990-2005, imports of FDA-regulated products increased from 2 million to 15 million lines per year -- an extraordinary 650 percent increase -- the majority of which are food. We now import more than 15 percent of our food supply. To meet this crushing tide of food imports, along with inspections of the domestic food industry, Congress appropriated only a 13 percent increase in Field personnel. With inadequate resources to handle these burgeoning imports, FDA now conducts a brief visual review of less than one percent of imports and conducts an actual physical examination for less than a tenth of one percent.

Realizing that this was untenable, in 2002 FDA proposed a science-based plan to reinvent food import regulation through use of scientific risk assessment and risk management techniques. Because it was estimated to cost \$80 million, however, the proposal did not make it through the Federal budget process. The resulting crises in adulterated and misbranded imported food during the past year have been the direct result of that decision. The \$80 million price tag for a new science-based import program -- which will cost at least \$100 million today -- is dwarfed by the hundreds of millions of dollars lost as a result of the failure to implement this program.

In his recent Executive Order announcing an Interagency Working Group on Import Safety, President Bush stated that the current system must be fixed "within available resources." The truth is that the system cannot be fixed "within available resources," but this answer is not politically correct and thus undoubtedly will not make it through the political process. Unless we are willing as a country to appropriate at least \$100 million for the scientific personnel and analyses needed to devise and implement a new food import system, we will retain the antiquated version we have now and will continue to witness the crises that we have seen in the past year.

FDA needs to develop the same type of science-based inspection program for domestic establishment inspections that it developed (but was not allowed to implement) for import inspections. Implementation of an adequate domestic inspection program would, of course, cost substantially more than the projected cost of the import inspection program. Without such a science-based plan, and the means to implement it, the country will continue to experience increased food safety problems -- such as the episodes of pathogens in spinach, lettuce, tomatoes, and peanut butter, and botulism in canned food, during the past year.

Imports of legitimate products are not the only problem confronting FDA’s Field staff. The import of counterfeit drugs -- as well as the manufacture of counterfeit drugs at domestic establishments posing as compounding pharmacies -- are overwhelming the Field inspection personnel. For example, Field inspectors had to trace the source of a million ineffective counterfeit diabetes test strips from the affected patients through 700 pharmacies, eight wholesalers, and two importers, to their ultimate source in China. A substantial increase in the FDA Field force is needed just to handle the growing number of counterfeit products.

Following the attacks on September 11, 2001, Congress appropriated increased funds and personnel for 2002, which allowed FDA to hire 673 new employees to improve its capacity to respond to the potential for terrorist threats and attacks regarding all FDA-regulated products. More than 60 percent of this supplemental appropriation was allocated to food. By 2006, however, all of this funding and personnel had disappeared from FDA appropriations. The number of Field personnel regularly performing inspections of imports fell from 531 in 2003 to 380 in 2006. There are 326 ports in the United States through which FDA-regulated products can enter the country. Obviously, FDA must deploy larger numbers of inspectors in the busiest of these ports, such as New York and San Francisco. Thus, there are many ports where FDA has no inspectors at all.

Because of its increasing responsibilities and its stagnant number of personnel, as well as a lack of travel funds, FDA cannot afford to send many inspectors abroad to investigate problems at their source. In 2000, FDA inspected 887 foreign establishments. By 2006, this was reduced to 738, a cut of 17 percent. Although approximately 80 percent of the active pharmaceutical ingredients used in our prescription drugs are imported from abroad, and foreign imports of drugs and active pharmaceutical ingredients were valued at more than \$42 billion in 2006, FDA conducted only 361 foreign drug and biological product establishments in 2006. Only 32 Field inspections were made in India and 15 in China, the two largest sources of pharmaceutical exports to the United States. Millions of shipments of FDA-regulated products are imported into the country each year from foreign facilities that have never been inspected by FDA and, with current appropriations, never will be.

Because of the reduced resources available to the FDA Field force, court enforcement actions have dwindled:

FDA Court Enforcement Cases			
	Seizure	Criminal	
		Injunction	Prosecution
1991	168	21	43
1992	183	31	52

FDA Court Enforcement Cases			
	Seizure	Criminal	
		Injunction	Prosecution
1993	117	23	26
2004	10	13	0
2005	20	15	0
2006	17	17	0
2007	6	12	0

Administrative compliance actions have suffered the same fate:

FDA Warning Letters	
1991	832
1992	1,712
1993	1,788
2004	725
2005	535
2006	538
2007	467

A weakened FDA inevitably leads to weak compliance with the law.

Conclusion

We must all recognize that FDA can increase its attention to high priority issues, or take on entirely new responsibilities, only in the following two ways. First, FDA can divert personnel from other priorities, thus leaving those other areas neglected. This is what happened with contaminated pet food, one of the many areas which have been neglected because of a lack of agency resources. Second, Congress can determine to provide adequate funding for all of the responsibilities that the country expects FDA to implement. But it is clear that, unless Congress adopts this second approach, FDA will of necessity be forced to follow the first.

Science is at the heart of everything that FDA does. Without a strong scientific foundation, the agency will founder and ultimately fail. The scientific resources needed by FDA to carry out its statutory mission cannot be sustained on a minimal budget. Congress must commit to doubling the current FDA funds, together with a 50 percent increase in authorized personnel, within the next two years. From then on, it is essential that the FDA budget at least keep up with inflation and perhaps even more. Another report should be prepared in five years to offer advice on the state of science at FDA at that time and the resource needs that remain.

Table 1 – Statutory History of FDA Regulatory Jurisdiction and Authority 1988–2007

The following compilation of 1988–2007 federal statutes includes only those for which the Food and Drug Administration (FDA) has been specifically delegated administrative responsibility by the Secretary of Health and Human Services and those that specifically direct the Commissioner of Food and Drugs or the agency to participate in federal action. It excludes those statutes that merely renumber the sections in the United States Code or rename the appropriate officials or agencies involved, as well as statutes of general applicability that apply to all federal agencies and are not specifically delegated to FDA. For omnibus statutes that cover more than one FDA-regulated product category (such as the FDA Modernization Act of 1997, the Bioterrorism Act of 2002, and the FDA Amendments Act of 2007), the major components are listed separately.

Year	Statute
1988	Orphan Drug Amendments of 1988 102 Stat. 90 (April 18, 1988)
	Prescription Drug Marketing Act of 1987 102 Stat. 95 (April 22, 1988)
	Pesticide Monitoring Improvements Act of 1988 102 Stat. 1411 (August 23, 1988)

Year	Statute
	Clinical Laboratory Improvement Amendments of 1988 102 Stat. 2903 (October 31, 1988)
	AIDS Amendments of 1988 102 Stat. 3062 (November 4, 1988)
	Food and Drug Administration Act of 1988 102 Stat. 3120 (November 4, 1988)
	Generic Animal Drug and Patent Term Restoration Act 102 Stat. 3971 (November 16, 1988)
	Veterinary Prescription Drug Amendment 102 Stat. 3983 (November 16, 1988)
	Anabolic Steroid and Human Growth Hormone Amendments 102 Stat. 4230 (November 18, 1988)
1989	
1990	National Nutrition Monitoring and Related Research Act of 1990 104 Stat. 1034 (October 22, 1990)
	Sanitary Food Transportation Act of 1990 101 Stat. 1213 (November 3, 1990)
	Congressional Access to FDA Trade Secret Information Amendment 104 Stat. 1388-210 (November 5, 1990)
	Nutrition Labeling and Education Act of 1990 104 Stat. 2353 (November 8, 1990)
	Good Samaritan Food Donation Act 104 Stat. 3183 (November 16, 1990)
	Amtrak Waste Disposal Act 104 Stat. 3185 (November 16, 1990)
	Agricultural Products National Laboratory Accreditation Standards Act 104 Stat. 3562 (November 28, 1990)
	Organic Foods Production Act of 1990 104 Stat. 3935 (November 28, 1990)
	Safe Medical Devices Act of 1990 104 Stat. 4511 (November 28, 1990)
	Combination Products Amendment 104 Stat. 4526 (November 28, 1990)
	Food and Drug Administration Revitalization Act 104 Stat. 4583 (November 28, 1990)
	FDA Freedom of Information Act Fee Retention Amendments 104 Stat. 4584 (November 28, 1990)
	Anabolic Steroids Control Act of 1990 104 Stat. 4851 (November 29, 1990)
	Human Growth Hormone Amendment 104 Stat. 4853 (November 29, 1990)
1991	Nutrition Labeling and Education Act Technical Amendments 105 Stat. 549 (August 17, 1991)
1992	American Technology Preeminence Act of 1991 106 Stat. 7 (February 14, 1992)
	Generic Drug Enforcement Act of 1992 106 Stat. 149 (May 13, 1992)

Year	Statute
	Medical Device Amendments of 1992 106 Stat. 238 (June 16, 1992)
	Methadone Maintenance Amendment 106 Stat. 412 (July 10, 1992)
	American Technology Preeminence Act Amendments 106 Stat. 847 (August 3, 1992)
	Prescription Drug Amendments of 1992 106 Stat. 941 (August 26, 1992)
	Mammography Quality Standards Act of 1992 106 Stat. 3547 (October 27, 1992)
	Prescription Drug User Fee Act of 1992 106 Stat. 4491 (October 29, 1992)
	Dietary Supplement Act of 1992 106 Stat. 4500 (October 29, 1992)
1993	FDA Employee Education Loan Repayment Amendments 107 Stat. 210 (June 10, 1993)
	Nutrition Labeling and Education Act Amendments of 1993 107 Stat. 773 (August 13, 1993)
1994	Nutrition Labeling and Education Act Amendment of 1994 108 Stat. 705 (May 26, 1994)
	Animal Medicinal Drug Use Clarification Act of 1994 108 Stat. 4153 (October 22, 1994)
	Maple Syrup Preemption Amendment 108 Stat. 4154 (October 22, 1994)
	Dietary Supplement Health and Education Act of 1994 108 Stat. 4325 (October 25, 1994)
1995	Edible Oil Regulatory Reform Act 109 Stat. 546 (November 20, 1995)
1996	National Technology Transfer and Advancement Act of 1995 110 Stat. 775 (March 7, 1996)
	Repeal of Saccharin Notice Requirement 110 Stat. 882 (April 1, 1996)
	Repeal of the Tea Importation Act of 1897 110 Stat. 1198 (April 9, 1996)
	FDA Export Reform and Enhancement Act of 1996 110 Stat. 1321-313 (April 26, 1996)
	Export of Partially Processed Biological Products Amendments of 1996 110 Stat. 1321-320 (April 26, 1996)
	Food Quality Protection Act of 1996 110 Stat. 1513 (August 3, 1996)
	Prescription Drug Medication Guide Amendment 110 Stat. 1593 (August 6, 1996)
	Saccharin Study and Labeling Act Extension Amendment of 1996 110 Stat. 1594 (August 6, 1996)
	Import for Export Amendment 110 Stat. 1594 (August 6, 1996)
	Bottled Drinking Water Standards Amendments 110 Stat. 1684 (August 6, 1996)

Year	Statute
	Health Insurance Portability and Accountability Act of 1996 110 Stat. 1936 (August 21, 1996)
	Good Samaritan Food Donation Act 110 Stat. 3011 (October 1, 1996)
	Repeal of Cardiac Pacemaker Registry Requirement 110 Stat. 3031 (October 2, 1996)
	Electronic Freedom of Information Act Amendments of 1996 110 Stat. 3048 (October 2, 1996)
	Comprehensive Methamphetamine Control Act of 1996 110 Stat. 3099 (October 3, 1996)
	Animal Drug Availability Act of 1996 110 Stat. 3151 (October 9, 1996)
	Drug-Induced Rape Prevention and Punishment Act of 1996 110 Stat. 3807 (October 13, 1996)
1997	Food and Drug Administration Modernization Act of 1997 111 Stat. 2296 (November 21, 1997)
	Prescription Drug User Fee Amendments of 1997 111 Stat. 2298 (November 21, 1997)
	Pediatric Drug Testing and Labeling Act of 1997 111 Stat. 2305 (November 21, 1997)
	The Prescription Drug Modernization Act of 1997 111 Stat. 2309 (November 21, 1997)
	The Biological Products Modernization Act of 1997 111 Stat. 2323 (November 21, 1997)
	The Medical Device Modernization Act of 1997 111 Stat. 2332 (November 21, 1997)
	The Food Modernization Act of 1997 111 Stat. 2350 (November 21, 1997)
	The General Provisions Modernization Act of 1997 111 Stat. 2356 (November 21, 1997)
1998	Food Safety Research and National Conference Amendments 112 Stat. 606 (June 23, 1998)
	Biomaterials Access Assurance Act of 1998 112 Stat. 1519 (August 13, 1998)
	Mammography Quality Standards Reauthorization Act of 1998 112 Stat. 1864 (October 9, 1998)
	Animal Drug Combination Ingredient Amendment 112 Stat. 2681-30 (October 21, 1998)
	Methamphetamine Trafficking Penalty Enhancement Act of 1998 112 Stat. 2681-759 (October 21, 1998)
	Antimicrobial Regulation Technical Corrections Act of 1998 112 Stat. 3035 (October 30, 1998)
	Repeal of Annual Report on Radiation Control for Health and Safety Program 112 Stat. 3285 (November 10, 1998)
1999	Healthcare Research and Quality Act of 1999 113 Stat. 1653 (December 6, 1999)

Year	Statute
2000	<p>Hillary J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000 114 Stat. 7 (February 18, 2000)</p> <p>Autoimmune Diseases Amendments 114 Stat. 1153 (October 17, 2000)</p> <p>Research in Children Amendment 114 Stat. 1167 (October 17, 2000)</p> <p>Drug Addiction Treatment Act of 2000 114 Stat. 1222 (October 17, 2000)</p> <p>Methamphetamine Production, Trafficking, and Abuse Act of 2000 114 Stat. 1228 (October 17, 2000)</p> <p>Rapid HIV Tests Amendment 114 Stat. 1354 (October 20, 2000)</p> <p>Medicine Equity and Drug Safety Act of 2000 114 Stat. 1549A-35 (October 28, 2000)</p> <p>Prescription Drug Import Fairness Act of 2000 114 Stat. 1549A-40 (October 28, 2000)</p> <p>Needlestick Safety and Prevention Act 114 Stat. 1901 (November 6, 2000)</p> <p>Human Papillomavirus Education Amendments 114 Stat. 2763A-72 (December 21, 2000)</p> <p>Condom Labeling Amendment 114 Stat. 2763A-73 (December 21, 2000)</p> <p>Repeal of Saccharin Study and Labeling Act 114 Stat. 2763A-73 (December 21, 2000)</p>
2001	<p>Animal Disease Risk Assessment, Prevention, and Control Act of 2001 115 Stat. 11 (May 24, 2001)</p>
2002	<p>Best Pharmaceuticals for Children Act 115 Stat. 1408 (January 4, 2002)</p> <p>Toll Free Number in Drug Labeling Amendment 115 Stat. 1422 (January 4, 2002)</p> <p>Catfish and Ginseng Labeling Amendments 116 Stat. 526 (May 13, 2002)</p> <p>Food Pasteurization Amendment 116 Stat. 530 (May 13, 2002)</p> <p>Food Irradiation Labeling Amendment 116 Stat. 531 (May 13, 2002)</p> <p>Accelerated Approval of Priority Bioterrorism Countermeasures Amendment 116 Stat. 613 (June 12, 2002)</p> <p>Food Safety and Security Amendments 116 Stat. 662 (June 12, 2002)</p> <p>Drug Safety and Security Amendments 116 Stat. 675 (June 12, 2002)</p> <p>Prescription Drug User Fee Amendments of 2002 116 Stat. 687 (June 12, 2002)</p> <p>Drug Postmarketing Studies Amendments 116 Stat. 693 (June 12, 2002)</p>

Year	Statute
	Medical Device User Fee and Modernization Act of 2002 116 Stat. 1588 (October 26, 2002)
	Rare Diseases Orphan Product Development Act of 2002 116 Stat. 1992 (November 6, 2002)
2003	United States Leadership Against HIV/AIDS, Tuberculosis, and Malaria Act of 2003 117 Stat. 711 (May 27, 2003)
	Blood Safety Report Amendments 117 Stat. 902 (August 15, 2003)
	Animal Drug User Fee Act of 2003 117 Stat. 1361 (November 18, 2003)
	Defense Biomedical Countermeasures Amendments 117 Stat. 1680 (November 24, 2003)
	Emergency Use of Medical Products Amendments 117 Stat. 1690 (November 24, 2003)
	Pediatric Research Equity Act of 2003 117 Stat. 1936 (December 3, 2003)
	Abbreviated New Drug Application Amendments 117 Stat. 2448 (December 8, 2003)
	Importation of Prescription Drugs Amendment 117 Stat. 2464 (December 8, 2003)
	Report on Importation of Drugs Amendment 117 Stat. 2469 (December 9, 2003)
2004	Medical Devices Technical Corrections Act 118 Stat. 572 (April 1, 2004)
	Project BioShield Act of 2004 118 Stat. 835 (July 21, 2004)
	Minor Use and Minor Species Animal Health Act of 2004 118 Stat. 891 (August 2, 2004)
	Food Allergen Labeling and Consumer Protection Act of 2004 118 Stat. 905 (August 2, 2004)
	Anabolic Steroid Control Act of 2004 118 Stat. 1661 (October 22, 2004)
	Mammography Quality Standards Reauthorization Act of 2004 118 Stat. 1738 (October 25, 2004)
2005	Patient Safety and Quality Improvement Act of 2005 119 Stat. 424 (July 29, 2005)
	Medical Device User Fee Stabilization Act of 2005 119 Stat. 439 (August 1, 2005)
	Methadone Treatment Amendments 119 Stat. 591 (August 2, 2005)
	Sanitary Food Transportation Act of 2005 119 Stat. 1911 (August 10, 2005)
	Contact Lens Amendment 119 Stat. 2119 (November 9, 2005)
	Stem Cell Therapeutic and Research Act of 2005 119 Stat. 2550 (December 20, 2005)

Year	Statute
	Public Readiness and Emergency Preparedness Act 119 Stat. 2818 (December 30, 2005)
2006	Combat Methamphetamine Epidemic Act of 2005 120 Stat. 256 (March 9, 2006)
	Biomedical Advanced Research and Development Act 120 Stat. 2865 (December 19, 2006)
	Dietary Supplement and Nonprescription Drug Consumer Protection Act 120 Stat. 3469 (December 22, 2006)
	Pandemic and All-Hazards Preparedness Act 120 Stat. 2831 (December 19, 2006)
2007	Food and Drug Administration Amendments Act of 2007 121 Stat. 823 (September 27, 2007)
	Prescription Drug User Fee Amendments of 2007 121 Stat. 825 (September 27, 2007)
	Medical Device User Fee Amendments of 2007 121 Stat. 842 (September 27, 2007)
	Medical Device Amendments of 2007 121 Stat. 852 (September 27, 2007)
	Pediatric Medical Device Safety and Improvement Act of 2007 121 Stat. 859 (September 27, 2007)
	Pediatric Research Equity Act of 2007 121 Stat. 866 (September 27, 2007)
	Best Pharmaceuticals for Children Act of 2007 121 Stat. 876 (September 27, 2007)
	Reagan-Udall Foundation for the Food and Drug Administration Act of 2007 121 Stat. 890 (September 27, 2007)
	Conflicts of Interest Amendments of 2007 121 Stat. 900 (September 27, 2007)
	Clinical Trial Databases Amendments of 2007 121 Stat. 904 (September 27, 2007)
	Postmarket Safety of Drugs Amendments of 2007 121 Stat. 922 (September 27, 2007)
	Food Safety Amendments of 2007 121 Stat. 962 (September 27, 2007)
	Food and Drug Administration Miscellaneous Amendments of 2007 121 Stat. 971 (September 27, 2007)

Table 2 – Representative Statutes of General Applicability that Have a Direct Major Impact on FDA 1935–2006

The following statutes do not specifically name FDA and have not specifically been delegated to FDA for implementation, but they have a substantial impact on the Agency.

Year	Statute
1935	Federal Register Act 49 Stat. 500 (July 26, 1935)
1946	Administrative Procedure Act 60 Stat. 237 (June 11, 1946)
1958	Small Business Act 72 Stat. 384 (July 18, 1958)
1966	Animal Welfare Act 80 Stat. 350 (August 24, 1966)
1967	Freedom of Information Act 81 Stat. 54 (June 5, 1967)
1970	National Environmental Policy Act of 1969 83 Stat. 852 (January 1, 1970)
1972	Federal Advisory Committee Act 86 Stat. 770 (October 6, 1972)
1974	Freedom of Information Act Amendments of 1974 88 Stat. 1561 (November 21, 1974)
	Privacy Act of 1974 88 Stat. 1896 (August 21, 1974)
1976	Government in the Sunshine Act 90 Stat. 1241 (September 13, 1976)
	Freedom of Information Act Amendments of 1976 90 Stat. 1247 (September 13, 1976)
1978	Carcinogen Testing and Listing Amendments 92 Stat. 3434 (November 9, 1978)
1980	Regulatory Flexibility Act 94 Stat. 1164 (September 19, 1980)
	Stevenson-Wydler Technology Innovation Act of 1980 94 Stat. 2311 (October 21, 1980)
	Paperwork Reduction Act of 1980 94 Stat. 2812 (December 11, 1980)
	Bayh-Dole Act 94 Stat. 3019 (December 12, 1980)
1981	Equal Access to Justice Act 95 Stat. 598 (August 13, 1981)
1982	Federal Managers Financial Integrity Act of 1982 96 Stat. 814 (September 8, 1982)
1984	Competition in Contracting Act of 1984 98 Stat. 1175 (July 19, 1984)

Year	Statue
1986	Federal Technology Transfer Act of 1986 100 Stat. 1785 (October 20, 1986)
	Freedom of Information Reform Act of 1986 100 Stat. 3207-48 (October 27, 1986)
1990	Chief Financial Officers Act of 1990 104 Stat. 2838 (November 15, 1990)
	Negotiated Rulemaking Act of 1990 104 Stat. 4969 (November 29, 1990)
1993	Government Performance and Results Act of 1993 107 Stat. 285 (August 3, 1993)
1995	Unfunded Mandates Reform Act of 1995 109 Stat. 49 (March 22, 1995)
	Paperwork Reduction Act of 1995 109 Stat. 163 (May 22, 1995)
	Federal Reports Elimination and Sunset Act of 1995 109 Stat. 707 (December 21, 1995)
1996	Information Technology Management Reform Act of 1996 110 Stat. 679 (February 10, 1996)
	Health Insurance Portability and Accountability Act of 1996 110 Stat. 1936 (August 21, 1996)
	Economic Espionage Act of 1996 110 Stat. 3488 (October 11, 1996)
	National Information Infrastructure Protection Act of 1996 110 Stat. 3491 (October 11, 1996)
1998	Government Paperwork Elimination Act 112 Stat. 2681-749 (October 21, 1998)
	Federal Reports Elimination Act of 1998 112 Stat. 3280 (November 10, 1998)
1999	Federal Financial Assistance Management Improvement Act of 1999 113 Stat. 1486 (November 20, 1999)
2000	Truth in Regulating Act of 2000 114 Stat. 1248 (October 17, 2000)
	Technology Transfer Commercialization Act of 2000 114 Stat. 1742 (November 1, 2000)
	Data Quality Act 114 Stat. 2763A-153 (December 21, 2000)
2002	Customs Border Security Act of 2002 116 Stat. 972 (August 6, 2002)
	E-Government Act of 2002 116 Stat. 2899 (December 17, 2002)

Table 3 – Representative Executive Orders of General Applicability that Have a Direct Major Impact on FDA 1969–2007

The following Executive Orders do not name FDA and have not specifically been delegated to FDA for implementation, but they have a very large impact on the Agency.

President	Executive Order
Nixon	Executive Order No. 11490 (Assigning Emergency Preparedness Functions to Federal Departments and Agencies) 34 Fed. Reg. 17567 (October 30, 1969)
Ford	Executive Order No. 11821 (Inflation Impact Statements) 39 Fed. Reg. 41501 (November 29, 1974)
	Executive Order No. 11921 (Emergency Preparedness Functions) 41 Fed. Reg. 24294 (June 15, 1976)
Carter	Executive Order No. 12044 (Improving Government Regulations) 43 Fed. Reg. 12661 (March 24, 1978)
	Executive Order No. 12174 (Paperwork) 44 Fed. Reg. 69609 (December 4, 1979)
Reagan	Executive Order No. 12291 (Federal Regulation) 46 Fed. Reg. 13193 (February 19, 1981)
	Executive Order No. 12372 (Intergovernmental Review of Federal Programs) 47 Fed. Reg. 30959 (July 16, 1982)
	Executive Order No. 12498 (Regulatory Planning Process) 50 Fed. Reg. 1036 (January 8, 1985)
	Executive Order No. 12512 (Federal Real Property Management) 50 Fed. Reg. 18453 (May 1, 1985)
	Executive Order No. 12600 (Predisclosure Notification Procedures for Confidential Commercial Information) 52 Fed. Reg. 23781 (June 25, 1987)
	Executive Order No. 12612 (Federalism) 52 Fed. Reg. 41635 (October 26, 1987)
George H.W. Bush	Executive Order No. 12689 (Debarment and Suspension) 54 Fed. Reg. 34131 (August 18, 1989)
	Executive Order No. 12770 (Metric Usage in Federal Government Programs) 56 Fed. Reg. 35801 (July 29, 1991)
Clinton	Executive Order No. 12861 (Elimination of One-Half of Executive Branch Internal Regulations) 58 Fed. Reg. 48255 (September 14, 1993)
	Executive Order No. 12862 (Setting Customer Service Standards) 58 Fed. Reg. 48257 (September 14, 1993)
	Executive Order No. 12866 (Regulatory Planning and Review) 58 Fed. Reg. 51735 (October 4, 1993)
	Executive Order No. 12875 (Enhancing the Intergovernmental Partnership)

President	Executive Order
	58 Fed. Reg. 58093 (October 28, 1993)
	Executive Order No. 12988 (Civil Justice Reform) 61 Fed. Reg. 4729 (February 7, 1996)
	Executive Order No. 13011 (Federal Information Technology) 61 Fed. Reg. 37657 (July 19, 1996)
	Executive Order No. 13083 (Federalism) 63 Fed. Reg. 27651 (May 19, 1998)
	Executive Order No. 13100 (President’s Council on Food Safety) 63 Fed. Reg. 45661 (August 25, 1998)
	Executive Order No. 13132 (Federalism) 64 Fed. Reg. 43255 (August 10, 1999)
George W. Bush	Executive Order No. 13327 (Federal Real Property Asset Management) 69 Fed. Reg. 5897 (February 6, 2004)
	Executive Order No. 13422 (Further Amendment to Executive Order 12866 on Regulatory Planning and Review) 72 Fed. Reg. 2763 (January 23, 2007)
	Executive Order No. 13439 (Establishing an InterAgency Working Group on Import Safety) 72 Fed. Reg. 40053 (July 20, 2007)

**Table 4 – FDA Appropriations and User Fees Part I
FY 1988–FY 2007 (\$ Millions)**

Fiscal Year	Human Drugs		Biologics		Medical Devices		Animal Food & Drugs	
	Center	Field	Center	Field	Center	Field	Center	Field
1988								
\$ Approp.	89.020	28.110	43.160	8.220	52.440	22.470	17.780	7.630
FTE Approp.	1,359	583	467	117	884	398	287	154
1989								
\$ Approp.	99.720	31.495	51.020	9.450	54.920	23.540	17.116	7.336
FTE Approp.	1,339	574	539	135	871	392	269	145
1990								
\$ Approp.	111.350	35.17	61.520	11.720	62.560	26.810	21.470	9.200
FTE Approp.	1,418	608	620	155	919	413	285	153
1991								
\$ Approp.	134.070	42.330	69.790	13.300	73.340	31.440	24.680	10.580
FTE Approp.	1,584	679	659	165	1,023	459	314	169
1992								
\$ Approp.	150.890	47.650	76.050	14.480	81.710	35.020	27.300	11.700
FTE Approp.	1,572	674	718	180	1,107	497	329	177
1993								
\$ Approp.	154.052	48.645	82.560	15.721	91.608	37.417	26.612	11.405
FTE Approp.	1,714*	735*	735	194	1,161	522	315	170
\$ User Fees	6.800*	2.150*	N.A.	N.A.	N.A.	N.A.	--	--
FTE User Fees	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	--	--
\$Total	160.852	50.795	82.560	15.721	91.608	37.417	26.612	11.405
FTE Total	1,714	735	775	194	1,161	522	315	170

"N.A." (Not Available) means that there is a number for this category but FDA is unable to provide it.

"--" means that there is no number for this category.

"*" means that this number for the category of Human Drugs includes funds or personnel obtained by user fees that were shared with the Center for Biologics Evaluation and Research, the Field, and other parts of FDA but FDA is unable to provide a further breakdown into these categories.

For 1988-1996, the breakdown between the Center and the Field is based on extrapolation from historical data.

1994								
\$ Approp.	150.490	47.522	107.180	20.411	111.551	47.808	28.223	12.095
FTE Approp.	1,743	747	882	221	1,169	630	322	173
\$ User Fees	30,360*	9.591*	N.A.	N.A.	N.A.	N.A.	--	--
FTE User Fees	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	--	--
\$Total	180.850	57.113	107.180	20.411	111.551	47.808	28.223	12.095
FTE Total	1,743	747	882	221	1,169	630	322	173

Fiscal Year	Human Drugs		Biologics		Medical Devices		Animal Food & Drugs	
	Center	Field	Center	Field	Center	Field	Center	Field
1995								
\$ Approp.	109.350	34.526	87.450	16.663	111.485	45.536	29.178	12,506
FTE Approp.	1,277	548	763	191	1,263	568	304	164
\$ User Fees	56.290*	17.774*	N.A	N.A	N.A	N.A	--	--
FTE User Fees	317*	136*	N.A	N.A	N.A	N.A	--	--
\$Total	165.640	52.300	87.450	16.663	111.485	45.536	29.178	12,506
FTE Total	1,594	684	763	191	1,263	568	304	164
1996								
\$ Approp.	153.540	48.484	73.340	13.975	100.600	35.945	25.810	11.061
FTE Approp.	1,476	632	643	161	1,106	497	262	141
\$ User Fees	38.660	12.203	25.190	4.801	5.990	5.733	--	--
FTE User Fees	246	105	165	41	30	13	--	--
\$Total	192.200	60.687	98.530	18.776	106.590	45.684	25.810	11.061
FTE Total	1,722	737	808	202	1,136	510	262	141
1997								
\$ Approp.	139.201	61.878	78.858	17.398	103.207	44.165	25.588	10.628
FTE Approp.	1,287	782	640	221	1,058	561	247	135
\$ User Fees	48.764	4.572	25.986	398	4.598	7.851	--	--
FTE User Fees	386	60	204	5	32	16	--	--
\$Total	187.965	66.450	104.844	17.496	107.805	52.016	25.588	10.628
FTE Total	1,673	842	844	226	1,090	577	247	135
1998								
\$ Approp.	139.201	57.378	78.35	17.744	104.311	39.175	29.375	12.598
FTE Approp.	1,241	784	644	231	1,030	493	264	164
\$ User Fees	56.499	5.924	26.095	511	8.653	5.158	--	--
FTE User Fees	404	69	187	5	32	19	--	--
\$Total	198.649	63.999	104.668	18.344	107.202	48.503	29.375	12.598
FTE Total	645	853	831	236	1,062	512	264	164
1999								
\$ Approp.	139.685	60,738	77.822	17.201	105.553	40.237	30.668	12.585
FTE Approp.	1,130	716	592	199	966	466	254	139
\$ User Fees	71.767	6,109	29.031	.311	4.957	8.261	--	--
FTE User Fees	551	59	195	3	32	16	--	--
\$Total	211.452	66.847	106.853	17.512	110.510	48.498	30.668	12.585
FTE Total	1,681	775	787	202	998	482	254	139
2000								
\$ Approp.	152.194	63.344	87.451	18.592	116.015	41.644	36.471	13.122
FTE Approp.	1,168	670	576	204	988	438	271	135
\$ User Fees	88.187	7.509	33.750	834	4.478	8.123	--	--
FTE User Fees	604	67	204	7	30	16	--	--
\$Total	240.381	70.853	121.291	19.426	120.493	49.764	36.471	13.122
FTE Total	1,772	737	780	211	1,018	454	271	135

Fiscal Year	Human Drugs		Biologics		Medical Devices		Animal Food & Drugs	
	Center	Field	Center	Field	Center	Field	Center	Field
2001								
\$ Approp.	151.468	67.047	86.215	22.088	121.972	43.334	48.440	15.630
FTE Approp.	1,140	684	561	225	986	442	290	152
\$ User Fees	96.995	6.970	36.217	2.710	3.900	8.359	--	--
FTE User Fees	644	67	248	7	30	15	--	--
\$Total	248.463	74.017	122.432	24.798	125.872	51.693	48.440	15.630
FTE Total	1,784	751	809	232	1,016	457	290	152
2002								
\$ Approp.	178.017	76.683	111.054	27.551	131.466	48.496	55.727	29.916
FTE Approp.	1,122	695	657	237	965	442	323	247
\$ User Fees	104.093	5.551	38.287	878	4.919	8.776	--	--
FTE User Fees	658	42	246	7	32	15	--	--
\$Total	282.110	82.234	149.311	28.531	136.385	57.272	55.727	29.916
FTE Total	1,780	737	894	242	997	457	323	247
2003								
\$ Approp.	188.837	85.236	117.391	27,927	140.429	52.921	57.115	30.544
FTE Approp.	1,159	761	701	246	968	464	341	255
\$ User Fees	125.103	4.672	47.116	1.002	14.692	9.243	--	--
FTE User Fees	742	34	274	8	35	18	--	--
\$Total	313.940	89.908	164.507	28.929	155.121	62.164	57.115	30.544
FTE Total	1,901	795	975	254	1,003	482	341	255
2004								
\$ Approp.	210.828	81.290	96.265	26.089	141.059	50.085	54.430	28.928
FTE Approp.	1,218	725	559	233	971	441	346	246
\$ User Fees	162.653	4.821	43.607	1.055	2.879	9.483	1.083	--
FTE User Fees	972	34	247	8	90	13	3	--
\$Total	373.481	86.111	139.872	27.144	161.938	59.568	55.513	28.928
FTE Total	2,190	759	797	241	1,061	454	349	246
2005								
\$ Approp.	210.481	85.003	96,595	26,514	163.292	51.670	55.360	35.124
FTE Approp.	1,171	666	553	215	970	397	330	241
\$ User Fees	185.555	5.095	46.435	1,140	19.865	9.945	7.538	--
FTE User Fees	1,049	32	265	8	134	15	39	--
\$Total	396.036	86.098	143.030	27.654	183.157	61.125	62.898	35.124
FTE Total	2,220	698	818	223	1,104	412	369	241
2006								
\$ Approp.	217.792	79.919	111.443	27.075	165.207	55.356	53.824	34.756
FTE Approp.	1,176	665	533	197	929	399	321	217
\$ User Fees	205.279	5.911	57.466	6.725	24.622	9.856	9.264	--
FTE User Fees	1,100	36	239	10	156	14	54	--
\$Total	423.071	85.834	168.909	28.800	189.829	65.212	63.088	34.756
FTE Total	2,276	701	772	207	1,085	413	375	217

Fiscal Year	Human Drugs		Biologics		Medical Devices		Animal Food & Drugs	
	Center	Field	Center	Field	Center	Field	Center	Field
2007								
\$ Approp.	230.757	84.381	116.005	28.542	172.258	58.425	58.355	36.394
FTE Approp.	1,186	604	592	190	935	386	324	209
\$ User Fees	248.350	6.888	62.069	3.669	29.503	12.734	9.537	--
FTE User Fees	1,134	37	251	11	163	15	54	--
\$Total	479.107	91.269	178.074	32.211	201.761	71.159	67.892	36.394
FTE Total	2,320	641	843	201	1,098	401	378	209

Table 5 – FDA Appropriations Part II FY 1988–FY 2007 (\$Millions)

Fiscal Year	Food		Cosmetics		NCTR	Total FDA Budget Authority
	Center	Field	Center	Field		
1988						
\$ Approp.	53.090	73.310	N.A.	N.A.	24.291	477.504
FTE Approp.	708	1,438	N.A.	N.A.	241	7,039
1989						
\$ Approp.	59.310	81.902	N.A.	N.A.	25.545	542.343
FTE Approp.	792	1,585	N.A.	N.A.	239	7,228
1990						
\$ Approp.	67.652	93.430	N.A.	N.A.	27.269	600.979
FTE Approp.	841	1,669	N.A.	N.A.	235	7,629
1991						
\$ Approp.	77.239	106.660	N.A.	N.A.	31.407	688.392
FTE Approp.	897	1,786	N.A.	N.A.	230	8,267
1992						
\$ Approp.	88.421	117.883	N.A.	N.A.	31.097	761.830
FTE Approp.	950	1,782	N.A.	N.A.	239	8,792
1993						
\$ Approp.	85.970	118.720	N.A.	N.A.	32.986	805.818
FTE Approp.	913	1,782	N.A.	N.A.	257	8,939
1994						
\$ Approp.	89.466	123.548	N.A.	N.A.	34.989	875.968
FTE Approp.	910	1,765	N.A.	N.A.	249	9,167
1995						
\$ Approp.	90.887	125.511	N.A.	N.A.	38.349	869.230
FTE Approp.	871	1,719	39	N.A.	247	8,811

Fiscal Year	Food		Cosmetics		NCTR	Total FDA Budget Authority
	Center	Field	Center	Field		
1996						
\$ Approp.	84.395	116.546	N.A.	N.A.	30.774	889.527
FTE Approp.	809	1,539	N.A.	N.A.	232	8,459

"NA" (Not Available) means that there is a number for this category but FDA is unable to provide it.

1997						
\$ Approp.	78.133	113.050	N.A.	N.A.	31.929	880.743
FTE Approp.	790	1,436	26	8	223	8,354
1998						
\$ Approp.	87.758	118.491	N.A.	N.A.	32.189	931.883
FTE Approp.	784	1,455	N.A.	N.A.	218	8,083
1999						
\$ Approp.	99.891	135.277	N.A.	N.A.	32.109	985.279
FTE Approp.	784	1,555	N.A.	N.A.	223	7,851
2000						
\$ Approp.	124.589	155.115	N.A.	N.A.	36.522	1,048.149
FTE Approp.	830	1,556	N.A.	N.A.	217	7,728
2001						
\$ Approp.	125.888	161.616	N.A.	N.A.	36.248	1,009.311
FTE Approp.	879	1,556	N.A.	N.A.	206	7,805
2002						
\$ Approp.	143.178	250.078	N.A.	N.A.	39.259	1,354.366
FTE Approp.	924	1,810	30	11	221	8,311
2003						
\$ Approp.	147.304	259.520	N.A.	N.A.	40.403	1,398.350
FTE Approp.	950	2,217	29	14	226	8,940
2004						
\$ Approp.	144.366	262.686	N.A.	N.A.	39.652	1,401.214
FTE Approp.	910	2,172	29	15	207	8,567
2005						
\$ Approp.	152.260	283.257			40.206	1,452.274
FTE Approp.	884	2,059	28	14	187	8,181
2006						
\$ Approp.	153.470	285.251	N.A.	N.A.	40.739	1,493.580
FTE Approp.	812	1,962	27	11	190	7,893
2007						
\$ Approp.	159.114	297.991	N.A.	N.A.	42.056	1,574.155
FTE Approp.	812	1,896	14	13	190	7,856

Table 6 – Regulated Industry Sales Statistics FY 1988–FY 2007

Fiscal Year	FDA Appropriations (\$ Millions)	Sales (\$ Billions)						
		Human Food	Rx & OTC Drugs	Biological Products	Cosmetics	Animal Feed & Drugs	Medical Devices	Total FDA Products
1988	477.504	563.520	40.848	N.A.	31.800	20.060	29.009	685.237
1989	542.343	600.375	45.055	N.A.	33.900	29.938	31.160	740.428
1990	600.979	649.094	50.683	N.A.	36.000	29.356	33.675	798.808
1991	688.392	677.414	54.870	N.A.	36.900	28.657	35.061	832.902
1992	761.830	682.912	58.159	N.A.	37.900	33.283	35.829	848.083
1993	805.818	710.825	61.675	N.A.	40.300	27.086	37.426	877.312
1994	875.968	742.565	65.086	N.A.	43.200	36.687	38.911	926.449
1995	869.230	766.761	71.760	7.707	45.900	32.090	40.948	957.459
1996	889.527	797.517	79.520	8.743	48.900	44.933	43.406	1,014.278
1997	880.743	838.927	88.753	10.049	51.600	41.255	45.767	1,066.302
1998	931.883	876.419	99.785	12.905	52.500	35.724	46.948	1,111.476
1999	985.279	924.534	115.978	17.136	53.900	36.192	48.755	1,179.359
2000	1,048.149	968.639	132.202	21.130	55.000	35.406	49.496	1,240.743
2001	1,009.311	1,011.876	150.064	26.627	54.400	35.708	49.944	1,302.992
2002	1,354.366	1,050.742	169.552	32.658	54.400	39.334	51.609	1,365.638
2003	1,398.350	1,098.961	186.899	39.239	56.000	44.038	54.733	1,440.631
2004	1,401.214	1,157.534	201.532	46.390	58.200	44.484	55.889	1,517.639
2005	1,452.274	1,230.793	212.520	54.846	61.700	43.177	58.072	1,606.262
2006	1,493.580	N.A.	N.A.	64.009	N.A.	38.303	N.A.	N.A.
2007	1,574.155	--	--	--	--	--	--	--

Center for Food Safety and Applied Nutrition (CFSAN)

1. Meeting Current Needs

A. Background

CFSAN, in conjunction with the Agency's field staff "is responsible for promoting and protecting the public's health by ensuring that the nation's food supply is safe, secure, sanitary, wholesome, and honestly labeled, and that cosmetic products are safe and properly labeled (FDA/CFSAN website)." Getting the science right is critical to CFSAN's ability to fulfill its mission. Decisions made in regulation development, pre-market approvals, legal actions, and food-related public health emergencies should be based on understanding of contemporary and emerging science within the context of the risk analysis paradigm. A substantial portion of CFSAN employees are scientists, physicians, engineers, and mathematicians who provide scientific review and advice in the course of their day to day work in the Agency and serve as a scientific resource that can be rapidly mobilized in public health emergencies. CFSAN acquires scientific information from a variety of sources including industry submissions, in-house laboratory programs, extramural sponsored research, academic-government-industry consortia, and through monitoring the scientific literature.

The products that fall under CFSAN's regulatory responsibility include most of the US human food supply, including dietary supplements, and cosmetics. (FDA regulates approximately 80 percent of food supply, which includes beverages and dietary supplements; excluded are meat products, poultry products and egg products, which are regulated by FSIS/USDA.). Many of the scientific issues that are dealt with across this broad product array share common characteristics and fall within the core activities described in materials provided by the Agency: except for a small class of food products, FDA does not have pre-market review of foods, but relies on targeted inspections, marketed product adverse event surveillance, and efficacy/safety assessment, and ensuring marketed product quality and safety.

In preparing this analysis, the Subcommittee read written reports of past advisory committee and other expert committee reviews, analyzed responses provided to the Task Force's questions, met with CFSAN staff on two occasions, and interviewed representatives of organizations knowledgeable of CFSAN programs. The latter group included staff of the Grocery Manufacturers Association and the International Food Information Council.

B. Current State Overview

The goal of the committee's analysis is to identify areas in which scientific effort do not adequately support FDA/CFSAN's important current regulatory activities and emerging future needs that current scientific activities are not well-positioned to address. The recent cascade of recalls related to fresh spinach, peanut butter, and melamine-contaminated pet food traced to Chinese wheat gluten and rice protein concentrate, and the subsequent investigation of poultry and swine fed contaminated pet food illustrates the inter-connectedness of the US food system and its vulnerability to contamination from pathogens and as well as imported ingredients. Much debate is ensuing, focusing on companies' and FDA/CFSAN's inability to detect and prevent the importation of adulterated ingredients. And as FDA/CFSAN begins testing ingredients imported from China intended for human food products and Congress holds hearings, the level of concern about the safety of the US food supply and FDA's ability to protect public health is expected to intensify.

The pet poisonings and cascading six weeks of recalls illustrate three weaknesses in the FDA/CFSAN system: lack of adequate statutory authority with respect to imported foods, lack of inspection resources, and lack of scientific capacity to detect contaminants never expected to be in food ingredients. Unlike meat and poultry products which can only be imported from countries in which an equivalent level of inspection is demonstrated. That lack of authority places higher demands on inspection at ports of entry, but FDA's inspection workforce is seriously understaffed, and less than 2 percent of imported foods are inspected. Finally, the ability to rapidly screen ingredients and foods for unknown toxic substances and pathogens is limited and represents a major challenge to both the Agency and to food companies.

Our major concern is identical to that voiced in 1990 by the Subcommittee on Foods, Cosmetics, and Veterinary Medicine: "There are deep concerns about the viability of the foods program and the lack of Agency priority for food issues. Declines in resources and program initiatives during the past 10–15 years indicate a lack of Agency management attention and interest in this area, although public interest in, and concern for, an effective food program remain high" (Report of the Subcommittee on Foods, Cosmetics, and Veterinary medicine, Appendix D, p. D-1). Despite infusions of resources under the Food Safety Initiative and post-9/11, CFSAN is struggling to conduct its public health regulatory mission in the face of diminished resources and burgeoning food imports. Additional scientific resources are desirable, but must also be accompanied by appropriate levels of inspection and enforcement support. A recent op-ed piece stated this finding in more compelling language: "The United States is sitting on a powder keg with uncontrolled importation and the distribution of low-quality food ingredients. Before it explodes — putting more animals and people at risk — corrective steps must be

taken.” (Peter Kovacs, former president of NutraSweet Kelco Co., It’s Not Just Pet Food, The Washington Post, April 23, 2007, p. A17.)

2. Current Resources

Since 2003, CFSAN’s workforce has declined from 950 FTE to 771 FTE in 2007. Projections for 2008 show a further decline to 756 FTE. In this same five-year period, many new responsibilities have been added. The new responsibilities include legislative mandates (e.g., FDAMA-food contact substances, Bioterrorism Act, FALCPA – food allergen labeling), regulatory initiatives (e.g., trans fatty acid labeling, egg safety, food cGMP), and emergency planning (e.g., pandemic influenza).

The dwindling resources are a severe impediment to CFSAN achieving its vision of being the world leader in food safety programs and science while maintaining a clear focus on protecting public. Other nutrition and consumer protections are low priority. Cosmetics safety is CFSAN’s lowest priority, with less than 20 FTE devoted to this area. CFSAN Director, Dr. Robert Brackett, acknowledges that CFSAN no longer has the ability to generate the science it needs in the area of human nutrition and must rely on what others provide.

3. Current Stressors

A. Overview

External and internal developments that pose the greatest stress on CFSAN’s ability to fulfill its mission include the following:

- Globalization of the food supply
- New and changing food processing technology
- New threats to public health
- New regulatory responsibilities
- Ongoing response to emergencies
- Unstable tool base
- Lack of resources to adequately support science, collaboration, outreach or compliance
- Old IT systems
- Lack of state of the art equipment
- Lack of expertise and depth of expertise
- Addressing ONLY the highest priorities

The two buy-outs offered in recent years to encourage voluntary early retirements have had the perverse effect of exacerbating CFSAN’s

scientific leadership problems, rather than freeing the Agency to recruit new scientific talent. Experienced scientific leaders took advantage of the buyouts and CFSAN has either been unable to replace them or replacements do not have the experience to make them most effective in their new positions. It should be noted that these voluntary retirements and early retirements were offered in order to meet the reduced funding allocations to CFSAN.

Following the 1999 review of CFSAN research programs conducted under the auspices of the Science Board, CFSAN implemented many innovations in its research program and management. More recently, CFSAN is proposing a reorganization of science to better lead and coordinate this important function. The Senior Science Advisor and Research Coordination functions will transfer to OCD to strengthen the science policy advice to the Center Director and to provide better strategic direction. A Research Coordination Team will coordinate the Center's research portfolio and forge partnerships and improve communication within FDA and with outside stakeholders.

B. Current State Assessment

1) Priority Setting

Under its current and immediate past Directors and in response to Congressional and Presidential requirements for strategic planning, CFSAN has developed and implemented long-range strategic plans. More importantly, on an annual basis the Director publishes the priorities for the coming year and seeks public comment. The careful thought built into this process is probably what has enabled CFSAN to maintain the high level of public health protection it has in the face of dwindling resources and growth in the numbers and volume of food and cosmetic products. However, the resource situation has become so severe that nothing beyond the top priorities can be accomplished. Many initiatives of public health importance cannot be undertaken until they reach a crisis situation.

2) Resources and Technology

CFSAN has five top priorities: ensuring food defense, ensuring food safety, improving nutrition, ensuring dietary supplement safety, and ensuring cosmetic safety. Within each of these priority focus areas, compliance, enforcement, regulation development, research, training epidemiology, risk assessment, emergency response and recovery, adverse events monitoring, education and outreach are all expected to be covered. Within food defense, priority is given to vulnerability assessments and preventive measures and shields. Within food safety, priority is given to responding to outbreaks, produce safety, egg safety, raw milk products, infant formula, and food-borne allergens. With nutrition, the major priority is food labeling modernization (including addressing obesity) and for dietary supplements, the priority is cGMPs.

In response to the Science Board's request, CFSAN identified seven examples where the scientific base needs to be strengthened through additional scientific expertise, additional resources, or through leveraging outside expertise (Task 2). CFSAN states that the "timeframe associated with these needs is short-term, i.e., within the next 18 months." The committee agrees that the needs are critical and immediate.

The seven priority areas are as follows:

- Food production sciences: Risk mitigation at the source
- Consumer understanding of nutrition and food safety information
- Regulatory programs to implement the Food Allergen Labeling and Consumer Protection Act (FALCPA) and advancing effective interventions
- Detection of food-borne viruses
- Prevention and detection of food-borne viral diseases
- Safety of cosmetics
- Adverse event reporting and analysis

The committee offers the following observations on these priorities:

- *Food production sciences:* Risk mitigation at the source – It is important for FDA to have scientific staff who can communicate with agricultural experts at USDA, state agencies, universities, and companies. However, this is an area of expertise where closer collaboration with USDA and university scientists may be more fruitful than a significant investment in developing horticulture and environmental science expertise. (This is discussed below under Collaboration/leveraging.)
- *Consumer understanding of nutrition and food safety information:* We agree on the importance of social and behavioral scientific expertise to CFSAN's ability to fulfill its roles related to labeling and risk communication (e.g., consumer guidance, outreach and education). The applications are specialized, and require thorough knowledge of food, making this an area where collaboration with staff in other FDA centers is desirable but not sufficient to meet CFSAN's needs.
- *Regulatory programs to implement the Food Allergen Labeling and Consumer Protection Act (FALCPA) and advancing effective interventions:* The committee agrees that CFSAN needs better understanding of and access to data on the size and sensitivities of the allergic population, especially allergen doses and distributions affected by current food processing practices.
- *Detection of food-borne viruses:* We agree with CFSAN's conclusion that the risk of viral food-borne diseases is huge, and

effective prevention strategies are hampered by limited scientific knowledge and resources devoted to the identification of viruses. Of particular relevance to the regulatory role, are the stated priorities of detection and techniques for genetic fingerprinting of food-borne viruses. This also is an area discussed further under Collaboration/leveraging.)

- *Prevention and detection of food-borne viral diseases:* The committee agrees that effective prevention and risk mitigation strategies, coupled to effective decontamination of food facilities involved in an outbreak are severely hampered by limited knowledge and resources. This also is an area discussed further under Collaboration/leveraging.)
- *Safety of cosmetics:* Cosmetics safety seems to always get short shrift, although one of the hottest areas of nanotechnology applications is in the cosmetics industry. The committee agrees that CFSAN is in need of expertise in this area.
- *Adverse event reporting and analysis:* When the Dietary Supplement and Non-Prescription Drug Consumer Protection Act goes into effect in December 2007, dietary supplement manufacturers will be required to report serious adverse events. This will permit CFSAN to conduct more active surveillance if the resources are available to access and analyze the data.

3) Science Expertise

In FDA's identification of self-assessed areas of scientific expertise needed, CFSAN has critical needs in all but two of the major areas of scientific expertise: life sciences, nanosciences, physical sciences, computing, health science, food science and social science. The two areas not identified as areas of critical need are engineering and manufacturing sciences.

CFSAN has been very innovative in developing new approaches to attract, retain and leverage scientific expertise, and should be commended for those efforts. For example, three FDA-academic-industry research centers (the Joint Institute for Food Safety and Applied Nutrition located at the University of Maryland, the National Center for Natural Products Research at the University of Mississippi, and the National Center for Food Safety and Technology/Moffet Center at the Illinois Institute of Technology). These collaborative research centers are examples of how FDA can leverage research in support of its regulatory mission, although it has been disappointing that overall output has been modest due to budget constraints on FDA's part and limited participation by industry. JIFSAN's contribution from CFSAN is now only \$750,000, as opposed to \$5 million at its inception. NCFST's budget is maintained at \$9 million through a congressional earmark and NCNPR is currently at \$2.5 million. These centers could be world leaders in establishing standards and procedures for assuring food safety, however they have not yet fulfilled that expectation.

CFSAN has ongoing relationships with several other universities which enables the staff to quickly access scientific talent. These include the University of California at Davis, the University of Georgia, the University of Michigan, and Texas A&M University.

Lack of resources has forced CFSAN to curtail its very effective extramural research grants program. Begun in 1998 as part of the Food Safety Initiative, funding grew from \$1.5 million to nearly \$4.5 million in 2003. No funds have been available in 2006 or 2007. The grants were designed as cooperative agreements, helping project officers to keep current with the fields of science while permitting the Agency an effective way to keep the targeted research oriented toward CFSAN's priorities.

4) Professional Development

Professional development and continuing education at CFSAN include mentoring programs, scientific seminars delivered on site and through "webinars", a professional development fund, and staff college courses. Some examples of course titles offered through the staff college are: Good Laboratory Practices for Scientists and Technical Staff, Critical Thinking in Analytical Laboratory Procedures for Food Microbiologists, and Risk assessment, Management, and Communication.

Department ceilings on attendance at domestic and international meetings have made it more difficult for CFSAN to provide opportunities for scientists to participate in professional and scientific meetings.

5) Collaborating/Leveraging

Additional resources for FDA inspections and new legislative authorities are being considered in Congress as potential fixes for the recent spate of high visibility human and pet outbreaks of food-borne disease.

Congress has not yet focused on the science base for policy and regulatory decisions in food safety and nutrition, even; although, in the long term, improving scientific understanding of food-borne hazards may be more important to public health (in developing effective interventions) than investment in more inspectors (once the inspection workforce is at a level of strength commensurate with its responsibilities). CFSAN has extremely limited research capabilities that have dwindled in recent years under intense budgetary pressures (evidenced by the zeroing out of the competitive grants program), and for much of its science base relies on the National Center for Toxicological Research (NCTR), and USDA (through ARS and CSREES) and NIH. Despite that reliance, CFSAN has little leverage over these research agencies to concentrate on CFSAN priorities, and CFSAN leadership is not satisfied with the existing mechanisms of interacting with, USDA and NIH to set research priorities. This is especially troublesome for NCTR, a sister organization within FDA.

The US has substantial research capabilities related to food safety and human nutrition. Between the Federal government and the Land Grant University systems, there is a huge capacity that could be brought to bear more effectively on scientific questions of strategic importance to CFSAN and the food industry.

The federal government supports about \$2 billion in agriculture research annually, split almost 50–50 between ARS's intramural laboratory system and CSREES' extramural programs. Both ARS (through its National Program Staff) and CSREES establish program priorities that take into account the needs of action agencies (FSIS, FDA, FCS, etc) along with other constituencies, although exactly how the final priorities are set is not clear. ARS holds an annual meeting to review food safety research progress and to hear the Agency's priorities for the future. An attempt was made to establish a Joint Institute for Food Safety Research to identify the ongoing research of relevance and provide a central point for priority setting across all the research agencies with food and nutrition portfolios, but that effort is now defunct. There is no way to easily identify ongoing intramural or extramural research of relevance to CFSAN's needs and priorities.

The Land Grant University system is home to an extensive array of scientific expertise that can be far more agile than the ARS labs in responding to emerging scientific issues. However, the very small amount of competitive grants funded through CSREES' National Research Initiative does not take advantage of this resource and is furthered hobbled by the restrictions imposed by Congress specifying its program priorities.

The Farm Bill is up for reauthorization which offers opportunity to re-orient USDA research priorities to better align with the needs of a science and risk based food safety regulatory system and the priorities that CFSAN has identified.

D

Center for Veterinary Medicine (CVM)

1. Background

The regulatory mission of CVM, and the scientific expertise required, maps across essentially all of the regulatory functions identified by the other major FDA regulatory Centers. CVM's mission is split into two areas related to the types of products regulated: 1.) companion animals (dogs, cats, horses and other pets) and 2.) public health impacted products and processes including food producing animals and other human food or product safety issues including: Antimicrobial resistance, BSE (Bovine Spongiform Encephalopathy – Mad Cow Disease), Biopharming (use of engineered animals to produce human drugs), Genetically modified (GMO) foods, and Human safety of animal feeds and additives.

The products being developed for use in both companion and food animal medicine are as sophisticated as those being developed for human medicine, yet are being regulated by a staff that is miniscule in proportion to the other Centers. The same scientific and bioinformatics skill matrix needed by every FDA Center maps onto CVM, yet they are severely understaffed to bring these modern scientific and technical tools to bear on its regulatory mission. The deficiencies and needs of human drug regulation extensively discussed in other sections of this report equally apply to CVM's animal drug regulatory mission.

CVM sees its primary mission as a Public Health Agency and thus has appropriately concentrated resources in these areas (e.g., drug residue test development, BSE detection, antimicrobial resistance assessment through NARMS (National Antimicrobial Resistance Monitoring System), safety of GMO foods, etc.). The passage of the Animal Drug User Fee Act has provided needed support to deal with review of companion animal products. This segment of the CVM-regulated portfolio is dramatically increasing as the population of companion animals (cats, dogs, horses, exotic pocket pets) skyrockets. For pet animals alone, this mission encompasses 73 million dogs, 90 million cats, 150 million fish, 17 million birds, 18 million small pets (so-called pocket pets like gerbils, hamsters, etc), and 11 million reptiles. In 2006, CVM received 16 new animal drug applications, some covering multiple species. These issues are addressed by approximately a staff of 375 individuals, less than 4 percent of FDA's total. Further constraining these funds is the fact that over 80 percent of this budget is allocated as salary.

Simultaneous with this review, the "Pet Food Poisoning" crisis hit and illustrates that despite the human public health focus, society expects and demands that CVM reacts to and prevent similar incidents in companion animal products. FDA received over 18,000 telephone calls concerning melamine pet food contamination. The pet food industry is

a \$15–20 billion a year business, and largely it falls within FDA's regulatory purview. It was estimated that about 1 percent of the total volume of pet food was involved with a potential economic impact of \$200 million. CVM has only two people working full time on pet food issues.

As is true for all of FDA, regulatory agencies must be reactive to crises, whether they be human drug safety (e.g., Vioxx), human food safety (e.g., bacterial contaminated lettuce, BSE) or animal safety (the current kidney toxicity melamine issue). This last incident also clearly illustrates other problems facing all of FDA which is the negative side of globalization where CVM provided data that 70 percent of bulk drug active ingredients, and probably a similar fraction of animal feed additives (wheat gluten) are from largely minimally regulated sources.

2. Current State Assessment

CVM has identified the following areas as their major regulatory issues requiring high levels of science:

- Residues and methods to identify them (chemicals and natural products), and emerging infectious diseases (e.g., BSE)
- Antimicrobial resistance monitoring (science and informatics basis of their NARMS program)
- Biotechnology (genetic engineering, cloning, use of phages for eliminating 0157 in meat, biopharming)
- Future new technologies involved in drug manufacturing or delivery (nanotechnology, genetics, biomarkers, new approaches to characterizing microbial resistance)

CVM has presented a deep understanding of the societal and scientific forces that are evolving over the next decade that may impact them. They correctly see the convergence of massive increases in data volume and complexity with the newly developed and focused products resulting from the "omics revolution" as manifested in the emergence of P4 medicine discussed throughout the body of this report which encompasses the developing discipline of Systems Biology (termed panomics by CVM). These two forces dramatically accelerate product development in all areas they regulate. They correctly see an increase in individual focused therapies that will integrate microcomputer processes, with novel engineered devices (nanomaterials, microfluidics) delivering individual therapies developed through P4 medicine applied to veterinary species. They correctly see the need for bioinformatics and integration of their databases both within CVM, across FDA and with other collaborating agencies. They also have unique databases (not structures) covering their regulated products with both target species endpoints as well as broader human public health endpoints.

However, there are issues and responsibilities facing CVM that are not clearly on many radar screens. One example is the safety of rendered products used in animal feeds relative to transfer of organisms (bacteria, BSE) or chemical toxins. This issue could dramatically increase when byproducts of the Biofuels industry begin to enter animal feeds destined for food animals. Approaches to deal with this must be thought out in advance, not after the first crisis hits.

They continue to lead development of the NARMS, a very successful collaborative program with USDA and CDC that was externally reviewed by the Science Board earlier this year. This program is making great strides but was hampered by IT and staffing limitations. CVM has also pursued applying Probabilistic Risk Assessment strategies to handle some of their more complex regulatory issues that do not fall neatly into regulations developed before these hazards or products were even conceived (e.g., BSE, nanotechnology), however CVM is bound by current regulations which restrict its full implementation. These data indicate that CVM recognizes crucial emerging trends in their regulated sectors but are hamstrung to address them by flat budgets and simultaneously emerging crises.

A problem with the flat-budget environment presently in effect at CVM is that COLA results in a reduced effort in areas that already require CVM attention. In NARMS, this results in a need to reduce sampling when in fact it probably should be expanded. This reduces morale and does not allow new resources to be applied to the crises of the day. Also, higher FDA Administration and Congress must be made aware that these individuals are not readily or quickly available to solve today's crises. Scientists with unique skill sets must work in the CVM environment to gain an appreciation of the product being regulated. Attending seminars alone will not accomplish these needs.

3. Key Stressors

CVM is woefully understaffed to address all of these issues. This was also evidenced by recent vacancies in key Division Directors (Food Safety and Production Drugs in CVM/ONADE; Compliance in OSC; Animal and Food Microbiology in OR), which were open when this report was being compiled. The individuals filling these positions need to be of the highest caliber. Incentives must be in place that would allow scientists from other disciplines to consider CVM an attractive environment in which to develop their careers. This is a challenge facing all of FDA, but is particularly acute with CVM as many top-level bioscientists would consider a veterinary dominated institute such as CVM an alien world. This will require a rethinking of CVM's research culture as well infusion of funds to support this environment. CVM is addressing this issue with a small Fellow program and their Staff College that allows outside experts to bring CVM scientists and reviewers up to speed on emerging science.

As documented in other sections of this report, CVM also faces the dilemma of addressing congressional unfunded mandates, an example being the Minor Use and Minor Species (MUMS) Animal Health Act of 2004. On the date of enactment (August 2, 2004), CVM was required to implement designation and conditional approval processes and subsequently publish implementing regulations. There was authorized to be appropriated \$1.2 million for fiscal year 2004, and such sums as may be necessary for each fiscal year thereafter, to oversee the development and legal marketing of new animal drugs for minor uses and minor species (the Office of MUMS); and there was authorized to be appropriated \$1M for the fiscal year following publication of final implementing regulations on designation, \$2 million for the subsequent fiscal year, and such sums as may be necessary for each fiscal year thereafter. The designation final rule just published on July 26, 2007. To date they have not received any funds. When one considers the relatively smaller size of CVM compared to other FDA Centers, this lack of appropriations for authorized projects significantly impacts CVM's ability to perform its underlying duties. When events such as the melamine pet food crises hits on top of this, they are crippled to adequately address their acknowledged mission.

The request to provide disciplines needed to address these areas are similar to that needed for all of FDA. A number of these needs should be met through collaboration with acknowledged experts or agencies, however the unique and diverse interspecies orientation of their mission requires in house expertise. This does NOT mean large in house research programs, but rather in house scientific expertise and knowledge. Disciplines that commonly appear on their matrix of needs include: biochemistry, bioinformatics, genetics, microbiology, molecular biology, toxicology, veterinary medicine, and risk assessment disciplines. These will need to be addressed by new hires, but also by continued expansion of their training initiatives as seen with their Staff College, as well as possibly by science exchange programs with academia and other FDA Centers and federal agencies sharing a similar skill set.

There is an immediate need to produce integrated IT database products and query software (not massive new hardware systems) to allow cross-CVM and FDA access to databases on pathogens, chemical toxicology, and adverse event reporting. Data needs to be electronically entered once, and subsequent databases populated electronically.

As is evidenced in the review of other centers from some individuals in the CVM-subgroup (CFSAN and NCTR), there is a crucial need for cross-center integration and sharing of resources. A commissioner level Chief Scientist with resources to apply to both emerging issues and crisis is needed.

4. Key Findings

- A. CVM is woefully understaffed and underfunded to address all of the diverse regulatory issues that define their core mission (companion animals, food safety (microbial, chemical and BSE, genetically modified foods) and bio-pharming as a few examples. This was evidenced by recent vacancies in key Division Directors. Incentives must be in place that would allow scientists from other disciplines to consider CVM an attractive environment in which to develop their careers.
- B. A problem with the flat-budget environment presently in effect at CVM is that COLA results in a reduced effort in areas that already require CVM attention. Coupled to unfunded mandates, these budgetary factors significantly reduce morale and does not allow new resources to be applied to the crises of the day. Also, higher FDA Administration and Congress must be made aware that these individuals are not readily or quickly available to solve today's crises (e.g., melamine, BSE, import safety). Scientists with unique skill sets must work in the CVM environment to gain an appreciation of the product being regulated.
- c. There is an immediate need to produce integrated IT database products and query software (not massive new hardware systems) to allow cross-CVM and FDA access to databases on pathogens, chemical toxicology, and adverse event reporting. Data needs to be electronically entered once, and subsequent databases populated electronically.
- D. As is evidenced in the review of other centers from some individuals in the CVM-subgroup (CFSAN and NCTR), there is a crucial need for cross-center integration and sharing of resources. A commissioner level Chief Scientist with resources to apply to both emerging issues and crisis is needed. There is continued need to increase collaborations and interactions with outside experts. This could include enhanced participation in the FDA Fellow program.

5. Recommendations

- A. Bolster in-house CVM scientific capability in areas of emerging product development in veterinary medicine as well as in addressing human safety of animal products under their regulatory purview, examples being BSE, GMO, Biopharming, and early detection of novel food contaminants such as melamine. The budgetary needs to accomplish these goals are proportionate to those identified for all of FDA in the body of this report.
- B. Bolster IT capability, including both seamless integration with other IT resources within FDA and with CVM partners (CDC,

USDA) as well as providing access to existing paper archives of drug approvals. A crucial need is to eliminate paper storage of CVM records not only to save storage costs (\$1 million per year), but more importantly, to allow quick retrieval of data.

- C. Foster integration with cutting edge science activities across FDA Centers and with external partners. However, this must be matched by recruitment of CVM specialists whom can serve as nodes for these interactions to ensure applicability to CVM's unique regulatory niche. The FDA Fellow Program should also be expanded to address this goal.

Center for Drug Evaluation and Research (CDER)

1. Summary of Findings

Based on the materials provided, the current state of CDER's scientific capabilities has glaring and troubling deficiencies. The rapid pace of advances in medical science requires a robust focused program to foster CDER reviewer confidence and support their intellectual growth as knowledge workers.

It is the sense of many in industry that the novelty and complexity attendant to cutting edge science can present significant challenges for CDER review staff. For them to efficiently and effectively review, particularly in the current "risk averse" environment, requires that the scientific foundation of staff is supported and nurtured. None of the examples provided demonstrate a strategic and sustained program of ongoing in-depth scientific and intellectual engagement that is up to the task of the submissions they face.

While this review focuses heavily on pre-market review, the issues raised here could be raised as well for post-market safety and surveillance, which are also heavily science based.

2. Background

This committee has been asked by the Commissioner to provide input on CDER scientific capabilities by providing an assessment of the current state, gaps and a recommended approach. CDER's mission is to ensure that Americans have access to safe and effective drug products of high quality. Data provided by the Center Director in January 2007 state that CDER has 2,360 staff on board, of which 1,794 are in scientific categories with a budget of 432 million.

Documents reviewed:

- Scientific Support of Regulatory Activities in the Center for Drug Evaluation and Research
- Core Competencies
- Response to Committee Questions
- 2006 listing of Scientific Training and CDER Scientific Educational Opportunities
- Office of Pharmaceutical Science Research Programs
- Regulatory Science and Review Enhancement Program
- Presentation by Dr. Galson and Dr. Von Eschenbach

3. *The Science Mission Overall*

A. Meeting Current Needs

As a “science based regulatory Agency”, CDER’s science mission must focus on activities which “ensure that drugs are safe and effective”. To adequately ensure safety and effectiveness requires understanding of the applicable basic science and clinical research. The drug development process encompasses a broad range of scientific needs from the pre-clinical (toxicology, pharmacology, biostatistics, underlying clinical science) to the clinical trials (therapeutic area specific knowledge, clinical trial design) and the post-marketing setting (e.g., epidemiology, social science, clinical practice).

The materials provided for review of the “current state” evidence an admirable, but insufficient effort by CDER. While it is clear what the mission is, *the current state of activities in support of this mission does not demonstrate careful planning or execution and lack a strategic and disciplined focus adequate to support the rapid advances in science CDER staff is faced with.*

B. Questions and Concerns

1. Core Competencies and Mastery: How do performance plans for review scientists ensure that CDER scientists based in the therapeutic areas are robustly engaged? How does CDER ensure that front-line regulatory scientists — those charged with reviews of the IND, NDAs and BLAs — continuously improve and refine their base of knowledge and its implications for regulation in their work with industry? Within a therapeutic area/review division, what standing mechanisms are in place to ensure that the knowledge base of the review disciplines is current and of sufficient depth, e.g., understanding of new findings in molecular mechanisms or pharmacogenomics, disease epidemiology, unmet needs in clinical care? There are only three journal clubs out of the 18 review divisions, many of which include multiple medical specialties.
2. The level of participation in professional associations, roundtables, CME accomplishments, or outcomes of time devoted to professional development activities is not clear.
3. For CDER scientific publications, it is not clear what internal peer review and clearance processes are in place to ensure the quality of publications generated by CDER staff.
4. We are aware of concerns from industry that the review divisions are at times ill prepared and appear not to be receptive to approaches which are not the “way things have always been done”. It is not clear that front line scientists are substantially included in Critical Path and committed to the risk that these novel approaches present to advance drug development science.

5. Given the rapid pace of change in the basic science — e.g., advances in understanding the molecular underpinnings of disease, new approaches in statistical methodologies — CDER faces significant challenges in meeting its unique role in ensuring safety and efficacy as these advances translate to the drug development process. Important opportunities to advance public health and meet unmet medical needs may be delayed or missed all together if the regulatory process becomes increasingly burdened due to a lack of receptivity to address these advances in a constructive collaborative engagement with regulated industry.
6. The materials provided did not evidence that CDER has a focused plan or program in place to develop its existing professional expertise within the scientific disciplines.

4. Science Infrastructure

A. Meeting Current Needs

1. *Science Expertise:* The data provided is inadequate to determine the adequacy of science expertise with any precision. CDER notes that there are 1,794 staff on board in scientific job categories ranging from medical officer (355), chemist (274), to mathematical statistician (109). It is impossible from this data to determine the actual expertise of staff in these categories.
2. *Professional Development:* The materials reviewed are vague in this regard. It appears that many of the medical officer staff are engaged in a half day professional development in clinical settings, not clinical research.
3. *Priority setting:* The current state does not demonstrate that priority setting has been done. This should be addressed as a gap going forward.
4. Resources and infrastructure:
 - CDER is faced with three major needs in science infrastructure — that of people, IT and knowledge management — and addressing CDER’s particular needs in test development or validation specific to product regulation and oversight (“the things that no one else can do or will do”). As part of HHS, the NIH has the major role in advancing basic and clinical research. AHRQ and CDC also have research missions in meeting public health needs relevant to their mission. Thus, collaboration beyond FDA must play a critical role in carrying out its mission with its sister agencies and with the academia.
 - CDER currently lacks a data management infrastructure that would optimize use of its extensive knowledge base of

submitted clinical trial data. We note that a major area of focus in the PDUFA IV negotiation is funding to improve the IT infrastructure.

- It is unclear how the OPS program prioritizes its work of regulatory relevant research and validation or to optimize its work through collaborative activities.
5. Collaborating/Leveraging (not meant to be comprehensive, but representative)
- *Within FDA:* There is insufficient data provided that within CDER or across Centers that a significant level of collaborative scientific activity is taking place.
 - *With other agencies:* AHQR and the CERTS program is a current example of collaborative activity. The NCI/FDA Initiative is another (recent MOU on the Janus Study Data Repository is an outcome of this activity).
 - *With industry:* the ongoing efforts under Critical Path — the Foundation for the NIH Biomarkers Consortium, the Predictive Safety Testing Consortium are examples under current state.
 - The Office of Pharmaceutical Sciences has collaborations with industry (e.g., PQRI) and with academic groups (e.g., NIPTE, MIT, Duquesne).

5. The Future of CDER and its Science

Staff from numerous groups within CDER have graciously committed their time to provide organizational overviews and respond to questions from the Science Board's subgroup charged with reviewing CDER's current and future science capabilities. The tendency is to presume that the scientific purpose is well-established to justify focusing attention on science "enablers," e.g., the personnel, staff training and IT tools necessary to carry out that purpose. From a cross-CDER perspective, absent is a clearly articulated, overarching science objective for CDER. This objective should guide the functions, activities and resources of the Center's components. It is futile to plan and prioritize CDER's future science capabilities without definition and agreement on how the science will be used.

CDER's focus should be on regulatory science, specifically the expertise to apply/interpret science and technologies to assess, accurately and expeditiously, the benefits and risks of medicines during the development, review and post-marketing surveillance processes. This is a tall order, but central to fulfilling CDER's public health responsibilities and the public's expectations. CDER should not aspire to be originator of basic science or unnecessarily the arbiter of it due to constrained resources and because these activities can be accomplished successfully in the academic and private sectors. A rigorous commitment to regulatory science to support sound decision

making will free up existing resources and, ideally, garner additional appropriations to meet CDER's increasing regulatory obligations. Among CDER's most pressing needs are sufficient IT infrastructure and "panomics" expertise.

CDER is typically engaged in reactive regulatory science in a problem-solving or fire-fighting posture. To keep pace with evolving science and resulting novel treatment modalities, CDER must transition to a culture of proactive regulatory science. Proactive regulatory science necessitates new thinking and new approaches to advance the development, registration and surveillance of important new medicines to meet critical public health challenges. These challenges include neurodegenerative and psychiatric diseases (among other therapeutic areas) with huge unmet medical needs, e.g., Alzheimer's disease, stroke, depression, and schizophrenia. However, emphasis is growing on certain CDER functions, like generic drug approvals and standard reviews of late entrants into a therapeutic class, which are statutory responsibilities but are not proactive regulatory science priorities. CDER must clearly draw such distinctions in the allocation of its resources. Appropriation funding could then enable critical regulatory functions, rather than replace resources for lower scientific priorities.

Fortunately, CDER has commendable experience and success with transforming itself to respond to new priorities. Crisis brings clarity of purpose as demonstrated by HIV/AIDS which underscored a desperate need to retool regulatory process and the scientific underpinnings for the development, review and surveillance of life-saving drugs. The accelerated approval process is a noteworthy example of the leadership role and impact CDER can have with progressive regulatory science.

Another application of proactive regulatory science is expediting the availability of important new medicines with accompanying rigorous pharmacovigilance measures for real-world and real-time safety monitoring. Although this is a policy issue that might be considered out of the purview of the Subcommittee, this concept of an expedited, "provisional" approval mechanism coupled with extensive safety monitoring did not originate from the subgroup's review of CDER's science. In fact, a prototype is addressed in the Government Accountability Office's (GAO) November 2006 report: "New Drug Development – Science, Business, Regulatory and Intellectual Property Issues Cited as Hampering Drug Development Efforts" (pp. 35–36) and in the published literature.

It is noteworthy that the findings by the GAO, the investigative body of Congress, reflect input from interviews with FDA staff, academics, public interest groups and pharmaceutical companies. Thus, a significant base of support for the provisional approval concept appears to exist, mostly likely buttressed by the success of accelerated approval in the HIV and Oncology arenas.

An example of how a provisional approval concept might work is abacavir, an antiretroviral indicated for the treatment on HIV-1. Abacavir went through the accelerated approval process thus the drug was made available to patients while long-term data to support its subsequent full approval were generated. During development and clinical use, hypersensitivity reactions were reported in some patients receiving abacavir. The first response was to implement a clinical vigilance program to alert prescribers and patients to early signs of hypersensitivity so that the drug could be promptly discontinued and never restarted. The second initiative to address the safety of abacavir was retrospective and then prospective pharmacogenetic studies by the sponsor to identify genetic markers predictive of patients at risk of hypersensitivity reactions from the drug.

The abacavir scenario, like the provisional approval concept, allowed patients in need of new treatments access to the effective drug while the drug was monitored through clinical vigilance and the application of evolving pharmacogenetic science to enhance the safety profile. What is especially noteworthy about the abacavir example is that because the drug was made clinically available, academics and others were able to study the drug's safety. Most significantly, the genetic variant associated with hypersensitivity found by the sponsor *was independently and contemporaneously identified by an academic group*, lending substantial confidence in the association. These efforts led to a clinically relevant, confirmed diagnostic for hypersensitivity responses to the drug with extremely high specificity [>99 percent] including several pharmacovigilance trials. The diagnostic is currently being used by many physicians treating HIV patients *before exposure to the drug* to avoid serious adverse events.

The provisional approval concept merits consideration and emphasis as a meaningful step towards the public health goal of making important new medicines with demonstrated efficacy available quickly while their safety is rigorously monitored. It also could provide CDER with a near-term opportunity to progress the transition from reactive to proactive regulatory science which is where the Center needs to be for the future. When science works and patients are protected, CDER must be at the forefront of the endeavor.

6. Critical Path

A. Introduction

The Critical Path refers to a strategic plan initiated and presented by senior FDA administrators during the period when Mark McClellan was the Commissioner. The set of documents that were subsequently developed mapped the strategic intent, and eventually outlined 76 specific critical path areas covered by the FDA that need attention. Despite the years of Acting leadership, there has been a serious commitment in sustaining momentum for the Critical Path initiatives,

primarily due to heroic efforts by several senior FDA administrators. Since 2004, when the strategy was published, until now, there have not been sufficient resources to support the reorganization of the Agency and create the expertise needed to develop the vision. There have, however, been some remarkable successes that have been emulated internationally. The Critical Path initiatives have led to remarkable progress in some areas, but stagnation continues in many others. Transitioning the Critical Path strategy to alignment within the organization has been limited by the significant lack of congressional support to provide even the necessary resources to maintain operations while adding trained professionals in many areas who are necessary to bring the strategy to tactical reality.

As a senior level initiative without the resources to create a planned reorganization, several disconnections and competing accountabilities have been exacerbated. This is evident particularly in CDER by the apparent disconnections between the *de facto* strategic policies emanating at the Review Team level, and the disability to connect to strategic initiatives, like those outlined in the Critical Path. These disconnections and malfunctions will be described more specifically in section 4.

B. Critical Path Approach

1) The Current State of the Critical Path Initiative

The Critical path Initiative has been embraced within CDER enthusiastically with new pilot programs, consortia, and collaborations. It is operating as a pathway, but with inadequate new resources to focus systematically on several of the high priority opportunities. From an external viewpoint the excitement generated in 2004 seems to have stalled, to the extent that publications exist that question the effectiveness of specific Critical Path opportunities – as if they were resourced. The Subgroup was encouraged by the range of opportunities being considered by 2006, but much of the activity was in specific CRADAs, consortia and collaborations. It is actually remarkable that so much progress has been made, but optimal results that would lead to changes in process require investment and dedicated resources

One important CDER initiative, to highlight as an example, is the planned appointment of an Associate Director for Safety and a Safety Regulatory Program Manager to each Office of New Drug review division. These appointments respond to Critical Path initiative as well as the Institute of Medicine's recommendations for improving drug safety review. The program is focused on addressing key needs/challenges for next 5+ years, but the recruitment of personnel and pilot projects are slowed by the lack of additional resources. Similar important CDER challenges consistently lack sufficient new investment to establish effective programs quickly. This is an important cause of the appearance of "stalled" initiatives. An important

difference between government and private responses to the need for new initiatives is the private sector's ability to change its labor mix – new resources can replace obsolete resources who were trained to use the very processes that need replacement. The reality that jobs are protected and that re-training without established new processes is virtually impossible, severely limits the ability of CDER to drive recognized and needed change.

Driving change from the top can be extremely effective, as long as the means to effect those changes are available. Regarding the response to the IOM Report that the Offices of New Drugs and the Office of Surveillance and Epidemiology (OSE) do not work well together, the FDA had the resources to only initiate two pilot projects that involve OSE personnel in drug reviews to determine the “logistics and value” of doing so rather than changing the role of the safety expert from occasional consultant to vital participant in the day-to-day work of regulatory decision making. This extremely important opportunity illustrates the difficulties of the Critical Path to gain rapid traction and speed within the Agency around one of the most critical elements of the Critical path – ensuring safety of medicines.

The enthusiasm for attending to Critical Path items is present among staff. Nevertheless, many Critical Path projects and pilots have been initiated at risk. None is adequately resourced. The margin of error is huge and brittle, with failure of any particular activity exemplifying failure for the Critical Path. From an external point of review, the failure of Congress and the Executive Branch to agree on adequate new support, but instead simply adding expensive new procedures of dubious value, is reflected in the initial efforts of the Agency to respond to the Critical Path promise.

2) Additional Needs for Sharper Focus, More Resources

The list of responses to the Critical Path Initiatives appears to be diffuse, unfocused and includes too much dependence on the assumption of good will from other Agencies or private partners. With a long list of unmet needs, it is difficult to focus sufficient scarce resources on any particular opportunity. In fact, the underlying difficulty is the lack of resources to focus on any particularly important relevant initiative, without shutting off the ability to include the many Critical Path opportunities that fall into the sphere of CDER interest. Key needs requiring attention and resources without diversion from current activities include the following:

Structure

CDER's current processes have markedly increased the burden on the Division Director, i.e., the leader responsible for ongoing review of a NCE IND and ultimately NDA (or BLA) for a new product. The Division is expected, indeed in some cases demanded, to consult with multiple other groups within FDA about a wide range of issues. While important

in some cases, expansion of the consultative processes have increased the coordination burden and increased the burden on the Director to take action on each consultation. From the sponsor's viewpoint, this makes decision-making authority in CDER more diffuse, results in unexpected emergence of new issues during development and particularly during review of an NDA (or BLA), and enables consultants to opine on an NDA (or BLA) when they have luxury of providing consultation without accountability for decision making. This phenomenon is widespread throughout Divisions and is one factor driving some FDA personnel toward consultative roles and away from reviewing roles.

Function

CDER's structure and processes, currently, as well as across the broader cultural environment, consistently and emphatically communicate to primary reviewers within FDA that the "safe" thing to do is ask for more information, ask for a new study, question the information from the sponsor, and delay or avoid granting approval decisions. The only Divisions that consistently have a different ethos are the Oncology group and HIV team within the Division of Antiviral Products, where these Divisions are routinely dealing with lifesaving medications. If you were working as a reviewer within FDA, you would quickly learn how to behave in order to go along and get along. This mindset, for example, has moved the development of novel antibacterial drugs to the threshold of extinction. Other pharmacologic classes will follow in time unless there is a change.

Prioritization

The FDA should clearly designate a list of indications that are viewed as important and have significant medical need, similar to current conditional mechanisms that have been successful for HIV and Oncology. These should automatically be given priority review and the Division should agree customized conditional/provisional approval requirements. This mechanism was clearly supported in the 2006 GAO document entitled "New Drug Development" as a means to accelerate innovative drug development using genomic technologies for individualized efficacy and extended studies sufficient to evaluate risk. It would replace current inadequate safety studies with larger, more long term conditional and surveillance programs, while modulating the burden on sponsors and regulators. There would be clear expectations for approval, and well defined observational safety studies, as well as specific efficacy determinations. This has been clearly demonstrated to be effective in HIV, where the Phase IV conditional program led to the designation and confirmation of a safety biomarker, along with prospective testing for positive and negative predictive value. With prioritization of conditional or provisional approval programs individualized for each product, each Review Division would not need its own unique, and sometimes unpredictable, responses.

After with drug development experts (e.g., academia, pharma and FDA) for suggestions on how to reduce costs, increase speed and encourage innovation, GAO concluded that collaboration was an advantageous approach:

“Collaborative efforts among government, industry and academia to identify diseases in great need of treatment, and implement an expedited regulatory process using conditional approval To help ensure safety, the drugs would have conditional approval – they would initially be distributed to certain populations whose usage of the drug can be studied and carefully monitored before wider distribution would be allowed.” (**“New Drug Development** – Science Business, Regulatory and Intellectual Property Issues Cited as Hampering Drug Development Efforts,” Government Accountability Office, p. 35–36, Nov. 2006.)

As another example of process that is ineffective, Exploratory INDs have contributed very little as the scope is to evaluate several compounds at the same time, pick the best, withdraw the exploratory IND and then submit a new IND for the selected molecule seems less than pragmatic. The reality is compounds rarely (<5 percent of cases at best) become available at the same time for this mechanism to work, the toxicology burden suggests a 14-day rodent and a confirmatory non-rodent study with full GLP reports — seems excessive duration in most cases and summary-type information as might exist in a CIB would seem adequate for the innocuous studies outlined in the guidance. This is not a pragmatic step to reduce regulatory burden. Even current FDA guidelines suggest single-dose studies in 2 species followed by a 14 day observation period will allow single-dose studies in humans and the IND does not need to be withdrawn but can be built upon.

Oversight

The mechanism for oversight at the functional level is overwhelmingly placed in the Division Director level. Oversight and consistency is difficult to effect, and the Voluntary Genomic Data Submission process, albeit not decisional, has been an effective means of providing education and discussion that is usually reflected at the Divisional level when those officials are available to attend.

The Advisory Committee process offers little value in proving useful insight and oversight. Unfortunately, in many cases, a public Advisory Committee meeting is more theater and public policy, than scientific discourse. It is increasingly difficult for FDA to engage the “best and brightest” to advise them and undermines fundamental purpose for advisory committees.

3. Lack of Mechanisms to Ensure Critical Path Initiatives are Consistent with Agency-Wide Requirements and Needs

The Critical Path Initiative is described in Agency-wide documents and, as such, delineates those areas specific to the Centers. With respect to CDER, there are several sets of initiatives that underlie the regulatory functions of CDER. Some of the CDER-specific additional needs are summarized above. But, the Critical Path is viewed by the IPRG as involving Agency-wide requirements. The critical needs are those related to the ability to drive a consistent and coherent strategy to the rest of the organization. The independent operation of Review Divisions that develop actions that ignore or disregard overall Agency goals, strategy, and new areas of regulatory science, and are inconsistent with the Critical Path strategic directions, point out the need for major structure and process alignment and accountabilities.

There is a variable disconnection between many of the Review Divisions and the centralized processes. As an overview of CDER, as the example, the disconnections are exacerbated by increasingly "local" and Advisory decisions that provide the external view of the FDA's view. The allocation of resources within CDER for the review of innovative project of major disease areas is supposed to be accelerated by the PDUFA [industry] funding. However the several-fold increase in dealing with increasing numbers of applications for generic products over the past several years is not reflected by adding additional funding for the beneficiaries of that activity – it comes at the expense of innovative products. Staff is spread so thin that consultation time for innovative new products is limited.

Center for Biologics Evaluation and Research (CBER)

1. *CBER's Mission and Vision*

CBER's mission is to ensure the safety, purity, potency, and effectiveness of biological products including vaccines, blood and blood products, and cells, tissues and gene therapies for the prevention, diagnosis, and treatment of human diseases, conditions, or injury. Through its mission, CBER also helps to defend the public against the threats of emerging infectious diseases and bioterrorism. CBER's vision is to use sound science and regulatory expertise to protect and improve public and individual health in the United States and, where feasible globally; facilitate the development, approval of and access to safe and effective products and promising new technologies; and strengthen CBER as a preeminent regulatory organization for the biologic products that fall under its regulatory authority, i.e., whole blood, blood derivatives and blood components, vaccines, somatic cell and gene therapy, allergenic extracts, xenotransplantation and tissue therapies.

As with the other Centers of the US FDA, CBER develops, maintains and supports a high-quality and diverse workforce; ensures compliance with laws and regulations through review, education, surveillance and enforcement; but is preeminent within FDA in conducting research as an essential element of science-based decision making.

A. Background

In preparing this analysis, members of the Subcommittee met with CBER senior staff on three occasions, two of those at CBER, read written reports of past advisory committees and other expert committee reviews, reviewed the extensive documentation provided by each of the five CBER offices (blood research and review; vaccine research and review; cellular, tissue, and gene therapies; biostatistics and epidemiology; compliance and biologics quality), analyzed the responses provided to the Subcommittee's questions and interviewed representatives of organizations knowledgeable of CBER programs. The latter group included: Dr. Jesse Goodman (Center Director), Dr. Karen Midthun (Medical Deputy Director), Dr. Kathryn Carbone (Associate Director for Research), Dr. Celia Witten (Director, Office of Cell, Tissue, and Gene Therapy-OCTGT), Dr. Suzanne Epstein (Associate Director for Research, OCTGT), Dr. Norman Baylor (Director, Office of Vaccines Research and Review-OVRR), Dr. Michael Brennan (Associate Director for Research, OVRR), Dr. Jay Epstein (Director, Office of Blood Research and Review-OBRR), Dr. Chintamani Atreya (Associate

Director for Research, OBRR), and Dr. Mary Malarkey (Director, Office of Compliance and Biological Quality-OCBQ).

The Subcommittee probed the organizational aspects of CBER and particularly paid attention to CBER research successes and potential forces that could limit such successes in the future.

The guiding principle of CBER research is that it be of high quality, efficient, and directed and managed to provide outcomes that address scientific and regulatory challenges in product development, safety, efficacy and quality that cannot or are not being met by the regulated industry. The CBER research program is highly collaborative and includes laboratory, epidemiological, statistical and clinical sciences and its scope encompasses the scientific basis of pre-clinical and clinical studies, manufacturing, regulatory submissions, inspections, post-marketing surveillance and Guidances. For fiscal year 2006 CBER had 979 FTEs, of which 772 were in the Center, and 207 in the field, with a total program support of \$197.7 million. Of the Center staff 334 (43 percent) held doctoral degrees (216 PhDs, 71 MDs, 17 MD/PhDs, 16 Doctorate of Nursing, three PharmDs, nine JD and two DVM).

In fiscal year 2004, a total of 216 FTEs were transferred from CBER to CDER; 84 of those FTEs were PDUFA fee paid positions and 128 were Salaries and Expenses FTEs. A total of \$27.6 million was transferred from CBER to CDER. This includes payroll and operating dollars, of which \$9.3 million was from PDUFA fees and the remaining \$18.3 million was from salaries and expenses. CDER reimburses CBER for four to eight FTEs a year depending on the level of support provided for animal care, IT, Resource Information Management (RIMS) and facilities. Approximately \$1 million is transferred back to CBER from CDER for these activities.

Approximately, 10–15 percent of CBER staff are “Researcher–Reviewers” who devote substantial time to research. All of the staff who do research (i.e., those termed Researcher–Reviewers) do both review and research with their time spent divided approximately 50 percent to research and 50 percent time devoted to review activities. Research–Reviewers are generally considered the CBER “product” experts whose research is focused on their product expertise area (e.g., childhood vaccines, blood products, gene therapies, etc.). The distribution of these Research–Reviewers within the various Offices show that about 50 percent are in vaccines, 30 percent in blood and 20 percent in cell, tissue and gene therapy.

In response to the Subcommittee’s question the Center identified 42 areas of Researcher–Reviewer expertise falling under the categories: virology; bacteriology; parasitic and unconventional agents; cell-tissue and plasma biology; manufacturing and emerging medical technologies.

B. Summary of Findings

The CBER review Subcommittee was impressed with the quality of science, the focused approach to regulatory science within CBER, the stability of the scientific staff within the Center, the strong commitment to priority setting and management processes, and the anticipation of the Center in moving forward in areas that likely will require expertise in the future. However, we are concerned with the lack of funding, the limited ability to provide professional development within such a resource restrained Agency and the potential for an issue of a changing environment when CBER moves to the White Oak facility.

2. Science Infrastructure

A. Scientific Expertise

As stated above, 42 different areas of scientific expertise for Research-Reviewers were identified for the Subcommittee. All areas of need and anticipated need appear to be included, but due to continuing budgetary restrictions, the number of individuals within each area of expertise is very limited, often with only one scientist identified. For example, nanotechnology and genomics were identified by CBER as areas of priority needs in the coming years, but only one and three Research-Reviewers PI scientists, respectively, can be presently identified with adequate expertise. The Subcommittee was concerned, for example, that only four PI scientists within CBER were identified with immunology expertise when this is a critical area of product evaluation within the area of Cell, Gene, Tissue and Plasma Biology. If 10–15 percent of the staff are research reviewers (RRs), and there are 42 different areas of scientific expertise, then there are only approx. 120 available RRs), only 2.9 RRs per science area. Thus the situation for nano and genomics is reduplicated throughout the Agency. Furthermore, in addition to the “cutting-edge” areas listed above, the areas of cell and tissue therapies are also expanding areas of science. There is certain to be increased applications for approvals in this area adding to the rather striking deficiencies in manpower and expertise posed by CBER’s functioning at the cutting-edge of human therapies.

B. Professional Development

This was an area of great concern to the Subcommittee. In response to questions about professional development it was emphasized that limited staff and limited budget prevented CBER scientists from engaging in professional development at the levels that the management and the scientists themselves would need. Furthermore, because of the limited scientific staff in any particular area of expertise, CBER product specialists were further restrained from participating in professional development activities when product submissions were received and PDUFA goals had to be met. Yet the

Subcommittee was impressed with the stability of scientists within the Center and the obvious *esprit de corps* that was evident in the presentations and scientific interactions with the Subcommittee.

C. Priority Setting

The Subcommittee was provided with an extensive list of research goals center-wide and in each of the Offices. The Subcommittee was provided with the fiscal year 2007 planning document for the fiscal year 2008 budget. Here by mid-year it is expected that Offices will update regulatory workload, public health portfolio analysis and scientific gap analysis and then provide the Center Director with updated Office research priorities. This then is translated in the office of the Center Director to an updated list of Center research priorities with each Office then providing individual research program reports that include achievements over the past year and the proposed research plan for the next year. The Center budget targets are then distributed by the office of the Center Director in late summer, revised with interactions through the various Offices with a final draft completed by the end of September. This draft of research priorities and budget is then presented for Advisory Committee input on the Office research plans.

The Subcommittee requested CBER to provide a detailed explication of how the malaria program was made a priority activity, the CBER response to this prioritization and how this prioritization affects other programs within CBER.

D. Resources and Technology

The Subcommittee was presented with an extensive list of CBER infrastructure needs categorized under the headings: General; Science and Science Innovation; Scientific, Technical and Medical Staff Development; Outreach, Communication, Partnerships and Leverage; Physical Plant needs; Computing and Information Technology needs.

As an example, one of the seven bullets under the heading Science and Science Innovation related to "improving capacity for safety and efficacy evaluations/monitoring of candidate and license products and to modernize current regulatory pathways and develop new regulatory pathways where there are currently none, through additional scientific expert staff, administrative support, space, research support and equipment to:

- Develop a Human Tissue Safety Testing Branch with a focus on tissue microbial safety
- Develop a multidisciplinary Vaccine Safety Team with a focus on candidate and licensed vaccines from initial development through clinical testing, licensure and post-licensure

- Develop a multidisciplinary Tissue Engineering team to work collaboratively with CDRH
- Develop a multidisciplinary CBER Personalized Medicine Team to develop/evaluate/validate/standards development for complex biological products, such as cell therapies, blood components (e.g., clotting factors), tumor vaccines, prophylactic vaccines.”

One of the seven bullets under Physical Plant needs states “adequate and appropriately designed and resourced laboratory space for research efforts, including BSL3+ laboratories.”

The Subcommittee was generally supportive of these infrastructure needs. CBER provided documentation of successes in a number of instances, some of which are described subsequently, where the science would not have been carried out except for CBER’s initiative. During one of its visits the Subcommittee was presented a case study related to work in the Agency on the safety and efficacy of hemoglobin-based oxygen carriers (HBOCs). It was recognized by CBER that preclinical safety and efficacy testing methods for HBOCs were limited and outdated, and that product failures were occurring during clinical testing phases. CBER developed better preclinical tests of oxidative chemistry, NMR and mass spectroscopy to predict safety and efficacy performance in clinical trials, thereby facilitating development of a technically challenging yet high potential public health value product. Draft guidance for industry detailing the criteria for safety and efficacy of HBOCs was prepared and presented to the Blood Products Advisory Committee. The public health impact of this work provided a clearer pathway to support more efficient development of safer, second generation HBOCs.

Currently, CBER has approximately 400,000 square feet of space in four research buildings. Two laboratory facilities have been completed at White Oak providing a current total of 167,470sf at White Oak. Total useable laboratory square footage at NIH and NLRC is 175,678.

E. Collaborating/Leveraging

CBER scientists continue to markedly interact with their colleagues who were transferred to CDER in fiscal year 2004. Strong interactions occur with CDER and CDRH due to the requirement of combination of products and devices used with CBER regulated products. Details of the budgetary interaction with CDER were presented above. CBER has extensive interactive relationships with NIH and CDC. The Subcommittee was told that approximately 70 percent of the non-FTE research personnel, research supplies and equipment money for research projects within CBER came from outside sources, mostly NIH.

3. Critical Path Approach

CBER provides leadership in the Critical Path research initiative. CBER's intramural, multidisciplinary disease and product oriented research programs are focused on challenges of unique priority to the FDA mission. CBER's intramural research regulators work collaboratively with government, academic and industry scientists with critical areas of expertise. And CBER takes advantage of extramural science and scientific efforts. All of these sources are used to contribute to Guidances, standards and regulatory decision making to support product development, safety efficacy assessment and review, as well as consistent manufacturing processes.

4. Management Structure/Processes

In 2002, CBER experienced a change in both Center and Research leadership. Over the past four years CBER completed external scientific Site Visit reviews of the CBER Laboratory Research Programs at the laboratory/researcher-reviewer and at the Office levels. Site visits are conducted through appropriate CBER Advisory Committees for each product office. Each Research-Reviewer PI receives a site visit every four years within a laboratory unit consisting of several PI research programs within a laboratory of the product offices. The subgroup evaluations are co-chaired by two Advisory Committee members and the evaluation is supplemented with appropriate outside scientific experts. Each PI prepares and submits site visit documents detailing achievements during the past four years and proposals for future research during the next four years, which is presented to the Advisory Site Visit Review Team. The Advisory Site Visit Review Team then holds individual interviews with each PI. The draft report is developed and finalized with presentation to and discussion by a full Advisory Committee vote. Formal responses to the comments within Site Visit reports are prepared and will be presented to Advisory Committees in the next year.

CBER scientific expertise and scientific contributions are critical to ensure the safety, effectiveness and availability of licensed biologic products, and play an important Critical Path role in facilitating biological product development and evaluation. Thus CBER initiated a Research Management Initiative to set a responsible, value driven course for the research, ensuring that research priorities and programs at CBER maintain the needed flexibility, infrastructure and collaborative scientific links to resolve regulatory challenges and emerging natural and man-made public health threats. In 2006 under the Research Management Initiative, CBER formed the CBER Research Leadership Council (RLC), composed of Research-Regulator and Regulatory Scientist leaders and managers from across the Center to develop and manage a formal research prioritization, planning and evaluation process within CBER. That process was described earlier in this report.

5. Examples of CBER Regulatory Sciences Successes

The following list documents only briefly a subset of regulatory science accomplishments that support the CBER model of science within the FDA. In general, CBER is in a unique position to: identify a cross-cutting issue; resolve scientific questions critical to regulation; to enhance the scientific quality of products reviewed; to maintain the capacity to investigate product failures; and to coordinate efforts across a spectrum of issues and companies involved in manufacturing biological products related to product characterization, safety and efficacy determinations and supply impacts. Some of these successes include:

- The lack of a blood donor test for West Nile Virus (WNV) – CBER laboratories developed and tested WNV standards and performed *in vitro* tests that supported policy making and guidance writing to safeguard the nation’s blood supply.
- Donor testing for Chagas disease – CBER-led intensive interactions with industry that facilitated the development, testing and licensure of an ELISA test to detect T.Cruzi antibodies in donors. This work was done in collaboration with WHO/PAHO, the American Association of Blood Banks and CDC.
- Transmission of transmissible spongiform encephalopathies (TSEs or “Prion diseases”) to humans from materials of human or bovine origin indicated a serious potential risk to recipients of biological products. An FDA Guidance in this area and many public meetings/workshops were initiated working together with NIAID/NIH, WHO, PAHO, academia, the American Red Cross and the NIBSC of the UK.
- Lack of standardized measurements for doses of adenovirus vectors led to difficulties in comparing different clinical trials in terms of dosing related adverse events and efficacy concerns. CBER led the partnership with industry and academia to develop an Adenovirus Reference Material (ARM) that is now available worldwide.
- CBER had been regulating musculoskeletal, skin and ocular tissues since 1993 but the focus was narrow. To ensure that the safety of newer cell therapies, such as reproductive cells and tissues and hematopoietic stem/progenitor cells, CBER needed to develop regulatory pathways for these products and advance the tissue rules. CBER proposed and finalized three rules that became effective in May 2005. In addition, CBER has published numerous Guidances for industry to help the tissue industry implement these rules.
- Safety of xenotransplantation and animal-sourced blood factors. Because of CBER’s scientists’ expertise in development of

important product quality tests, all xenotransplantation products are now rigorously tested for expression of infectious retroviruses.

- Home-Use HIV Test Kits – CBER virologists, epidemiologists and statisticians working together with CDC and NIH developed a set of acceptable standards for performance of these test kits and worked to insure that clinical testing could be performed efficiently and rapidly.
- Mumps – CBER testing and collaboration with NIBSC confirmed that current non-human primate neurotoxicity tests for mumps vaccine was not statistically predictive of human risk for vaccine-induced meningitis. A prototype pre-clinical neurovirulence safety test using rodents predictive of human risk for vaccine-induced neurotoxicity was developed by CBER and is being validated through a joint collaboration with WHO.
- Safety and efficacy of hemoglobin-based oxygen carriers (HBOCs). CBER developed better preclinical tests of oxidative chemistry, NMR and mass spectroscopy to predict safety and efficacy performance in clinical trials of HBOC products.
- Statistics innovations: simultaneous tests for non-inferiority and superiority – CBER statistical scientists developed and proved statistical methods for determining that clinical trial outcomes reflect product benefit and will better ensure product performance after licensure.

6. CBER Challenges in the Next Five Years

In the wake of huge increases in support for medical product discovery science, similar support is needed for FDA to maintain an advanced scientific expertise and to develop the new product evaluations science to efficiently review and support these new candidate complex biological products and facilitate their progress to marketed products. Infrastructure needs at CBER just to bring scientific capacity up to a realistic level of support are significant and overwhelming following years of funding challenges. However, the prioritizations formula now being utilized by CBER should identify the most critical needs and approaches. Yet the scientific infrastructure needs to advance and grow to prepare for current and future products. Support for adequate office and laboratory facilities at White Oak will be important. CBER products bring unique capacity to White Oak, but also challenges and resource needs. CBER scientists require BLS3+ labs and animal facilities for vaccines and blood product issues; NMR flow cytometry core and other unique equipment; quality assurance laboratories and the co-localization of research-regulatory and regulatory science staff. The CBER Subcommittee is concerned that the move from the NIH may be detrimental to the morale of CBER scientists who will then find themselves distantly located from their research collaborators on the NIH campus and from the many seminars and scientific expertise

available within the NIH. We anticipate that a significant management effort must be undertaken to address this potential problem.

CBER scientists have identified nanotechnology, genomics and advances in vaccine development as five year needs for increased resources. CBER does obtain funding for lot release, but insufficient for several initiatives needed for lot release. The ability for CBER to continue to fund its research programs through collaborations with NIH and CDC are critical five-year issues.

National Center for Toxicological Research (NCTR)

1. Key Findings and Recommendations

There were strong differences of opinion among members of the Working Group about how best to address the issues associated with NCTR. Some felt strongly that NCTR should not be part of FDA and the report should recommended separation. Others felt that other options were better, including bringing it closer to core FDA operations and functions.

NCTR research is unique in the following ways:

- High quality scientists and facilities providing unique capabilities responsive to FDA needs
- Scientists able to respond to FDA needs because of ability to deal with proprietary data as a part of FDA
- Ability to leverage resources through Cooperative Research and Develop Agreements (CRADA), InterAgency Agreements (IAGs) and collaborations with FDA Centers and ORA.
- NCTR's regulatory research always has the objective to determine the human health impact of FDA regulated products and is in response to:

Congressional earmark programs

FDA-sponsored research programs

- Center to Center interaction of management and scientists
- Scientist-initiated proposals for integrating emerging basic research into regulatory tools
- NCTR's research focuses on detection or prevention of toxicity and adverse events.

During the Subcommittee's deliberations an important development has occurred. The Office of the Commissioner will be moving NCTR into its domain allowing for more direct integration into the risk / regulatory paradigm.

2. Report of the Subgroup on NCTR

A. Introduction

The National Center for Toxicological Research (NCTR) was established in 1971, "to assist the Commissioner of the FDA in discharging his

responsibilities under the Federal FDC, the Fair Packaging and Labeling Act, and various provisions of the PHS Act". By Executive Order, the NCTR was established as a non-regulatory national resource owned and managed within DHHS by the FDA. The NCTR is located near Jefferson, AR on ~500 acres of land adjacent to Department of the Army's Pine Bluff Arsenal. It is a line item in the FDA appropriation that is part of the Agriculture submission. The NCTR, through IAGs such as the NTP/NIEHS and CRADAs, conducts collaborative research that leverages resources to address regulatory needs of the FDA.

The NCTR consists of about 30 buildings comprising about one million sq. ft. of floor space complete with such special facilities as BSL-3 level containment laboratories, other general and specialized laboratories, a vivarium for primates and non-primates, a unique photo-toxicology facility, and an onsite housing unit for visiting scientists. The NCTR employs over 500 workers and has an allocated FTE of 188, with a current headcount of 115 doctoral scientists. The NCTR is scientifically well equipped and capable of supporting Innovative cutting-edge research.

B. Findings

- Despite efforts to better integrate NCTR's programs with those of other Centers within the Agency, geography/distance continues to be an issue.
- The NCTR submitted suggestions to the Subcommittee for a means of establishing an Agency-wide process for prioritizing research that is used by NCTR with the other FDA Centers in leveraging resources from NIEHS to conduct safety and toxicity assessments of FDA nominated compounds to address specific regulatory issues.
- Safety Pharmacology studies at NCTR need to be expanded. An agreed upon priority setting process for all research in the Agency and increased funding for research is needed.
- Priority-setting within NCTR must be coordinated and compatible with those of other Centers within the Agency. This is an Agency issue. NCTR developed a strategic plan (2007-2011) that was vetted with the other centers to get agreement before it was issued in January 2007.
- The NCTR must be more supportive in assisting/supporting the programmatic needs of CDER, CFSAN, CVM and other Centers.

NCTR has a comprehensive peer review process for all protocols and each protocol is circulated to sister centers for review and modification to address their regulatory need or question.

- It is unclear why the 2007 Scientific Categories listing of job designations for 'toxicology' allocates only "2" for the NCTR out of a total of "40" throughout the remainder of the Agency. NCTR is

multidisciplinary and has a variety of scientific disciplines working together to solve complex scientific issues.

- NCTR has established a Systems Toxicology Division that specifically addresses the need for a systems biology approach for integrating new technologies with traditional endpoints. NCTR's Systems Toxicology Division includes Centers of Excellence in Toxicoinformatics, Metabolomics, Proteomics and Functional Genomics – all integrated to address critical path needs to integrate new technologies into the review process and assist in promoting personalized nutrition and medicine. NCTR expertise in this area has provided the infrastructure (ArrayTrack system) on which the VXDS program (CDER, NCTR and other Centers collaboration) has been developed.
- A new Division of Personalized Nutrition and Medicine has been launched to develop and validate a reviewer's tool kit for application to personalized health care.
- Since the NCTR has a non-regulatory charter, it should focus on new methods development and validation for the Agency. It is one of the Center's that can invest in technology and methods R & D.
- Selective intra-Center exchanges of key scientists assist in enhancing the Agency's programmatic integration. NCTR does this now and in the past. In fact NCTR hosted several scientists from CFSAN, CVM and CDER at the NCTR in the summer of 2007 providing training in ArrayTrack™ software, extraction methods, and micronucleus assays for use in genetic toxicology regulatory decision making.
- The NCTR's Science Advisory Board, while providing a valuable service, must be made more aware of scientific programs within CFSAN, CDER, CVM and other Centers to insure better coordination and integration. At each NCTR SAB meeting the NCTR requests other center representatives to present their mission and scientific needs in a brief overview.
- Although the NCTR has been quite effective in securing resources through IAGs, it has a tendency to detract from its primary mission. Historically, it is noteworthy that the NCTR has conducted comprehensive bioassays on FDA nominated compounds to assess safety and toxicity in support of the FDA regulatory needs. This is done via a Memorandum of Understanding and InterAgency Agreement between FDA/NCTR and NIEHS/the National Toxicology Program (NTP). The NTP is a program that examines safety/toxicology of drugs and food contaminants/supplements.

Importantly, toxicology protocols should be driven and supported by Centers like CDER, CFSAN, CVM, etc. — focus should be on contemporary drug and food safety

C. Recommendations of the Subgroup

- Enhance the incorporation of safety pharmacology in the NCTR's mission
- An Agency priority-setting process, such as the one currently used by NCTR in conjunction with the NIEHS/NTP program should be applied and coordinated across the Agency.
- NCTR is applauded for collaborative research that leverages funding from other agencies to support Agency regulatory need.
- Since the NCTR has a non-regulatory charter, the staff can focus on integrated research across program disciplines that provide identification of biomarkers of toxicity, development of new technologies to facilitate review, and new methods development and validation.

3. Science Success and Leveraging at NCTR

A. Personalized Nutrition and Medicine

1.) *MicroArray Quality Control (MAQC) Project* *Leveraged Research/Critical Path*

Microarrays represent a core technology in pharmacogenomics that was identified by the US Food and Drug Administration's (FDA) Critical Path Initiative as a key opportunity for advancing medical product development and personalized medicine (<http://www.fda.gov/oc/initiatives/criticalpath/>). However, a gap exists between technologies in use today and the technological levels required for application during product development and regulatory decision making. One of the concerns has involved the reliability of microarray technology because of the apparent lack of reproducibility between lists of genes (i.e., potential biomarkers) identified as differentially expressed from similar or identical study designs with different platforms or laboratories. The research performed by the FDA's National Center for Toxicological Research (NCTR) provides a sound scientific base addressing these concerns.

- MAQC – Phase I

The MicroArray Quality Control (MAQC) project (<http://edkb.fda.gov/MAQC/>) was initiated by the NCTR in February, 2005 in order to address reliability concerns as well as other performance, quality, and data analysis issues. One hundred and 37 scientists from 51 organizations including government agencies, manufacturers of microarray platforms and RNA samples, microarray service providers, academic laboratories, and other stakeholders designed a study plan. Two distinct, commercially available human reference RNA samples were generated and analyzed at multiple test sites using a variety of

microarray-based and alternative technology platforms, resulting in a rich dataset with over 1,300 microarray hybridizations including a toxicogenomic validation datasets. Findings from Phase I of the MAQC project were published in a series of peer-reviewed articles in *Nature Biotechnology*, September 8, 2006 (<http://www.nature.com/nbt/focus/maqc/index.html>). The MAQC project observed intra-platform consistency across test sites as well as high inter-platform concordance in terms of genes identified as differentially expressed. A two-page summary of the MAQC Phase I results can be found at (http://www.fda.gov/nctr/science/centers/toxicoinformatics/maqc/docs/MAQC_Summary_1stPhase.pdf).

- MAQC – Phase II

Phase II of the MAQC effort is designed to provide a realistic assessment of the capabilities and limitation of microarray technology in both clinical (diagnostic, prognostic, and individualized therapy) and toxicogenomic applications. A notice of solicitation for participation was published in the *Federal Register*, pp.20707–8, April 21, 2006.

The MAQC Phase II kickoff meeting was held at the NCTR/FDA, Jefferson, AR, in September 2006. Currently there are 136 participants from 66 organizations working in MAQC Phase II. Meeting summaries can be found at the MAQC project website at (<http://www.fda.gov/nctr/science/centers/toxicoinformatics/maqc/>). Five Working Groups (WGs) have been established and work concurrently during the MAQC Phase II: (1) Clinical WG, to focus on clinical applications; (2) Toxicogenomics WG, to focus on toxicogenomic applications; and (3) MAQC Titrations WG, to focus on the MAQC titration samples, (4) Regulatory Biostatistics WG to develop statistical analysis plans and (5) Genome-Wide Association WG to develop SNP-based classification models that are clinically predictive of outcomes. Meeting participants expressed strong interests in contributing to the MAQC Phase II, which is open to the public. The workgroups in this project have representatives from FDA, other government agencies, academic institutions, and a variety of industries including pharmaceutical manufacturers, software developers, and microarray providers. A primary goal of MAQC I and II and the Voluntary Genomic Data Submission program (VGDS) is converting “lessons-learned” from the program to best practice concepts for further advancing the field of PGx and its regulation, and serves as the basis of new guidance documents to industry such as “Guidance for Industry: Pharmacogenomic Data Submissions – Companion Guidance” Docket #7735 August 2007.

2.) *ArrayTrack™*

ArrayTrack™ is an NCTR-developed data management and analysis software with the capability to assess, process, and integrate microarray and traditional toxicological data. FDA reviewers are trained on the software and are using it as a pilot for assessing voluntary pharmacogenomic data submissions from industry to the Agency. Recently, the Gene Ontology for Functional Analysis (GOFFA) module of ArrayTrack™ was released. GOFFA uses gene ontology (characterization of genes and gene product attributes) for studying data from genomics and proteomics technologies

ArrayTrack™ is under continuous development and modules are being developed for metabolomics (metabolism) data. Future efforts include collaboration with industry to produce a commercial version for use in the drug-review process by pharmaceutical companies and regulatory agencies.

3.) *New Division of Personalized Nutrition and Medicine: Statistical Algorithms*

Biologists and biostatisticians have been assembled in the new Division of Personalized Nutrition and Medicine. The goal of this Division is to develop and validate a reviewer's tool kit to advance personalized public health. Toward this goal, NCTR scientists have recently developed new statistical algorithms called "classification ensembles from random partitions" (CERP) (Moon *et al.*, 2006) that use high-dimensional genomic and other input data to classify individual patients into risk/benefit categories. These studies demonstrate the real potential for confident clinical assignment of therapies on an individual-patient basis.

B. Food Safety Applied Research

1.) *Salmonella Typhimurium DT 104*

Investigation at NCTR on drug resistance in the highly pathogenic bacterium *Salmonella typhimurium* DT104, using strains from human and animal sources, has indicated that many strains are resistant to at least six antibiotics. Since this is a food-safety issue, the FDA needed adequate information on the prevalence of drug-resistant bacteria and the factors that contribute to their spread. The current methods for characterization of multi-drug resistant bacteria require several days. NCTR scientists developed a more sensitive and rapid PCR method to identify *Salmonella typhimurium* DT104 genes in clinical, food, and environmental samples that is now being used by field labs of the FDA Office of Regulatory Affairs to detect these bacteria in food samples.

2.) Antimicrobial Decision Tree

In collaboration with CVM, NCTR scientists have assessed the safety of antibiotics and their effects on the gastrointestinal tract resulting in the development of a decision tree for determining the limits on acceptable daily intake of antimicrobials in foods. This decision tree was adopted by the World Health Organization and used in the FDA Center for Veterinary Medicine's *Guidance for Industry #52*.

3.) Veterinary Antibiotic Resistance

A study by NCTR scientists has characterized antibiotic-resistant *Campylobacter* and *E. coli* strains from poultry meat and poultry litter with resistance to multiple antibiotics, supporting the theory that widespread usage of veterinary antibiotics can also induce antibiotic resistance in bacteria that infect humans. The bacteria were analyzed with molecular techniques (PCR restriction fragment length polymorphism and pulsed-field gel electrophoresis). The results were cited by the FDA's General Counsel during litigation over the decision of the FDA Center for Veterinary Medicine to withdraw the approval of two fluoroquinolone antibiotics used in veterinary practice. The prevalence of fluoroquinolone-resistant *E. coli* strains in poultry supports the theory that widespread usage of veterinary antibiotics can also induce antibiotic resistance in bacteria that infect humans.

4.) Research Collaborations with CFSAN

Established productive and ongoing research collaborations with CFSAN food safety/bioterrorism investigators to develop, test, and apply biochemical and biological assays for potential bioterrorism agents such as ricin, abrin, staphylococcus enterotoxins, *Clostridium botulinum* toxin, and other neurotoxins that are compatible with FDA-regulated foods to complement existing chemical and immunoassay systems.

5.) Assay for Ricin and Abrin

Developed a robust cell-based functional assay for the bioterrorism agents ricin and abrin compatible with FDA-regulated foods and applied the method to assess the residual toxin biologic activity following heat treatments in representative food matrices including infant formula, fruit juices, and yogurt cultures.

6.) Acrylamide Food Contamination

In collaboration with CFSAN and NTP/NIEHS, an ongoing study of the effects of lifetime exposure to the food contaminant, acrylamide, is currently underway and represents the state-of-the-art in terms of the comprehensive, repeated assessment of nervous system function across a variety of domains. The use of behavioral measures that are applicable to humans maximizes relevance for prediction of effects in humans. Concurrent neuropathological analyses compliment, expand and strengthen the risk evaluation.

C. Additional Leveraged Research

Research Description	Compound	FDA Center	Results
Toxicological assessment of pediatric sedative	Chloral Hydrate	CDER	CDER determined that the risk to pediatric patients undergoing medical procedures requiring the use of chloral hydrate was minimal and did not require additional labeling changes (TR-502,503)
Aquaculture drug safety	Malachite Green	CVM	Malachite green was found to cause liver tumors in rodents. CVM used this data in enforcement activities and in establishing residue hazard levels for unapproved animal drugs. The U.K. and some Asian governments used the data to establish aquaculture residue hazard standards. This animal drug remains unapproved for use in aquaculture. The use of malachite green has been significantly reduced as a result of these studies.
Food contaminant safety	Fumonisin B1	CFSAN	Data were used by CFSAN, USDA, CVM, Agriculture and Health Canada and by FAO/WHO Joint Expert Committee on Food Additives (JEFCA) for setting contaminant levels in grains used in both animal and human food products.
Beverage contaminant safety	Urethane/Ethanol	CFSAN	Data indicated that ethanol had a weak/mixed effect on the potentiation of urethane carcinogenicity. CFSAN has not yet conducted a risk assessment on urethane. The bioassay data have been used by a recent FAO/WHO Joint Expert Committee on Food Additives (JECFA) review of urethane.
Safety assessment of pyrrolizidine alkaloid herbal supplements	Riddelliine	CFSAN	This information was used by CFSAN to establish a warning about the consumption of dietary supplements which contain these alkaloids. Contaminant-safe dietary levels for the pyrrolizidine alkaloids were also established.

Research Description	Compound	FDA Center	Results
Relationship of exfoliating cosmetic ingredients to UV damage to skin	α & β Hydroxy Acids Glycolic Acid Salicylic Acid	CFSAN	Results of this study indicate no increase in sunlight-induced skin cancer in mice by either alpha or beta hydroxy acids.
Cosmetic ingredient safety	Retinyl Palmitate	CFSAN	Preliminary data furnished to CFSAN indicate that retinyl palmitate is likely equivocal for photocarcinogenicity.
Dietary supplement/cosmetic safety	Aloe Vera	NCI/CFSAN	Technical report under review by NTP but preliminary results suggested that the whole-leaf extract and gel enhanced the photocarcinogenicity of UV radiation.
Risk assessment of food contaminant	Acrylamide	CFSAN	Preliminary data confirm that acrylamide is genotoxic. Carcinogenicity studies are in progress from which FDA and WHO risk assessments will be conducted. Neurotoxicology studies suggest few behavioral effects of acrylamide.
Development of a PBPK/PD Model for Acrylamide	Acrylamide	Univ. of Maryland and CFSAN	A physiologically based pharmacokinetic model (PBPK/PD) has been designed and applied to extensive studies in male and female rats and mice; this same model is being utilized to interpret limited literature data in humans which will improve subsequent risk assessments.

Center for Devices and Radiological Health (CDRH)

1. Summary of Findings and Recommendations

A. Overall Findings

While progress has been made by CDRH to adequately utilize science in carrying out its mission over the past five years, without sufficient intervention the Center will have severe difficulties in carrying out its mission over the next decade.

B. Overall Recommendation

Develop and execute a plan for addressing deficiencies within CDRH's current science infrastructure and future planning, while integrating best practices throughout the FDA with CDRH's current structure. The plan should incorporate recommendations from this subgroup.

2. Introduction: Importance of the CDRH Science Mission

Science lies at the heart of all-important regulatory decisions at CDRH. Decisions that do not have adequate scientific support are thus relegated to delays, or worse, poor decisions can be made. The subgroup believes that CDRH has worked in earnest to carry out its scientific mission. The following examples illustrate some of the successes CDRH's research has had in accomplishing its mission (from the CDRH report entitled Science Prioritization Process).

A. Computational Fluid Dynamics of Left Ventricular Assist Device

CDRH laboratory expertise in experimental and computation fluid dynamics was utilized to aid in the evaluation of a post-approval study change for a pediatric left ventricular assist device (LVAD). The sponsor proposed to make a change to the blood flow path within the pump that could have adversely affected hemolysis and thrombogenesis in the pump such that patient safety and/or device efficacy could have been compromised. It would have been extremely difficult if not impossible to validate the design changes using animal or human data. After discussions and a meeting with FDA staff, the sponsor agreed to provide experimental (flow visualization, hemolysis) and analytical (computational fluid dynamics [CFD]) testing to support the design changes. CDRH experts recommended appropriate CFD models to the sponsors and analyzed the results. In this instance, our

efforts eliminated the need for the sponsor to perform expensive and time-consuming animal testing and/or clinical testing. The proposed design changes were approved, thus expediting the availability of this innovative device.

B. Computer-Assisted Diagnostic Systems

CDRH scientists have worked in the development of new models and methods for the assessment of computer-assisted diagnostic systems. The techniques were first developed during a review of digital mammography systems, and have since been extended to the development of systems for breast cancer screening, lung cancer screening, and CT colonoscopy. CDRH scientists who have developed these methods have played an important role on the review team for applications for these devices. Having these tools and methods available has greatly assisted developers of these innovative imaging and CAD-assist devices.

C. Performance Testing of Pulse Oximeters

CDRH scientists and engineers have developed test methods for a range of non-invasive monitoring devices. CDRH laboratory studies on pulse oximeter performance, for example, enabled substantial improvements in the ISO/IEC standard and the CDRH Guidance Document. This testing facilitated the development of a single test protocol for SpO₂ accuracy studies, which simplified the pre-market evaluation process by unifying the basis for establishing substantial equivalence. The work has established the groundwork to enable the extensions of claims being made for perfusion measurements and established acceptable performance criteria. In a related initiative, CDRH laboratory work on surface temperature properties was central in defining the limits for the General Standard for Electromedical Safety, 3rd edition of IEC 60601-1, and for the particular standard for the safety and essential performance of pulse oximeters, ISO/IEC 9919. CDRH laboratory scientists, working with industry experts, provided computational models and relevant literature that established that the existing limit could be relaxed by 2°C, making possible new device types and extending applications of existing devices. CDRH laboratory efforts were also instrumental in the establishment of a reliable test method for validating the design of pulse oximeter cables. This work is being incorporated in the next revision of the ISO/IEC standard.

D. Test Methods for High-Intensity Focused Ultrasound

HIFU holds the potential for radically advanced surgical techniques, including ablation of both malignant and benign lesions and cessation of internal bleeding in injured vessels and organs, all with minimal damage to the surrounding tissue. However, the lack of standardized methods to assess the acoustic and thermal characteristics of the

focused beams has challenged the regulatory review of these devices, especially in the pre-clinical phase, and has been burdensome to the industry. In the past CDRH scientists and engineers have developed measurement instrumentation and computational modeling techniques for characterizing other types of medical ultrasound devices such as diagnostic imaging and therapeutic ultrasound, and this work has resulted in the creation of numerous regulatory guidance and standards documents. This expertise is being used to accelerate the review of submissions for HIFU devices. For example, in a device for the ablation of uterine fibroids, CDRH-developed computational modeling was used to predict the performance of the device under conditions that would have been difficult to investigate experimentally, thus shortening the review time. CDRH laboratory staff members are now collaborating with outside research institutions and the affected industry to develop standard measurement and analysis methods as input to international standards for HIFU that will be used to facilitate the regulatory review process.

E. Guidance for Extracorporeal Shock Wave Lithotripsy

Extracorporeal shock wave lithotripsy is a minimally invasive technology that employs focused, high pressure, ultrasonic waves for fragmentation of kidney and urethral calculi. When first introduced, these devices were deemed Class III because of the new intended use coupled with the potential for serious collateral damage to non-targeted tissue. At the time there were no accepted means for measuring the very high pressures produced by these devices, which complicated the regulatory reviews. Based on CDRH laboratory efforts, performance requirements for measurement instruments and appropriate measurement procedures were developed and documented in a pre-clinical testing guidance for the industry. This guidance eventually led to two international consensus standards, which in turn were instrumental in allowing CDRH to down-classify these devices to Class II, thus saving the industry from lengthy human clinical trials.

F. Expediting Intraocular Lens Evaluations

OSEL laboratory scientists have played a leading role in the development of new test methods for measuring the optical parameters of intraocular lens implants (IOLs). An estimated 20 million Americans over the age of 40 have cataracts in at least one eye, most of which can be corrected through the implantation of IOLs. The focal length (or dioptic power) is a fundamental parameter whose precise measurement is of critical importance for evaluating the safety and effectiveness of IOLs. Testing the dioptic power of IOLs has been difficult because conventionally used test methods are limited in terms of accuracy and the dynamic range over which measurements can be performed. To overcome these problems, CDRH laboratory scientists developed a novel confocal fiber optic laser method (CFOLM) for precise measurement of IOL dioptic power that provides high accuracy

(exceeding 1 μm) in spatially locating the focal point and in measuring the IOL dioptic power. Such accurate measurements have not been achievable previously. The new CFOLM measurement system has been used to evaluate the dioptic power of a variety of new IOL designs from several different manufacturers, and to resolve questions about the accuracy of the labeled dioptic power, expediting decision making by facilitating agreement between industry and CDRH. This new test method will be considered for incorporation in international product performance standards for testing IOLs.

G. Spinal Implant Evaluation

FDA has received a dramatic increase in the number of submissions for new spinal implants, a sector of the orthopedic medical device industry whose revenues were estimated at \$3.6 billion in 2005, signifying an increase of 17 percent over the previous year. Under the auspices of MDUFMA, CDRH laboratories initiated a research program into vertebroplasty, a minimally invasive procedure for treatment of spinal compression fractures, with the goal of providing reviewers with better scientific information on the mechanical benefits of the treatment in order to accelerate and improve reviews of product safety and labeling. This laboratory initiative resulted in developing information clarifying the mechanical stability of the spine after this treatment that has substantially assisted CDRH's scientific review staff, enabling more efficient interactions with manufacturers and expediting the review process. CDRH laboratory membership has assumed the chairmanship of the ASTM Subcommittee F04.25 on spinal devices. In addition, CDRH laboratory scientists have provided the device reviewers in CDRH's Office of Device Evaluation with information on the use of these testing standards that, complemented with physical models of testing fixtures, has enabled improved understanding of how standard test methods are being used by device companies. This understanding has greatly facilitated their reviews of new products.

3. The Challenge of the Future

Will CDRH be able to adequately address its scientific mission, now and in the future?

A comprehensive 10-year CDRH technology forecast was developed in 1998, and a second one is currently in preparation. Based on the projections developed in the last two technology forecasts, the major medical-device technology areas in which significant developments are expected over the next decade includes:

- Aging-related devices
- Artificial organs and organ assists
- Computerized devices and intelligent systems
- Early diagnosis/detection technologies
- Genomics, proteomics, metabolomics, epigenomics

- Home- and self-care devices
- Imaging systems
- Minimally invasive technologies
- Miniaturization technologies
- Photonic technologies
- Portable and mobile devices
- Robotic devices
- Sensor technologies
- Telemedicine
- Wireless devices and systems

4. Summary of Findings

It is clear from this subgroup's review, that CDRH does not have the personnel or resources in place to adequately support the science needs in the regulatory review process for the planned technologies of the future described above. The list above therefore represents the technologies that may be hampered, or not reach their full potential unless interventions aimed at insuring that adequate CDRH Science support of the regulatory mission is achieved. In addition, while the technology forecast performed denotes good planning by management at CDRH, current plans and resources are not adequate to address unforeseen technologies developed in the future that have regulatory consequences.

5. The Science Mission

CDRH and its current ability to carry out its Science Mission. The Science Infrastructure and Management of CDRH.

On the face of it, the Center has made considerable efforts to effectively carry out its science mission via changes in its science infrastructure and organizational management. At the same time CDRH's science mission has been challenged by an ever-changing list of technologies, and the convergence of biological, chemical and mechanically integrated products.

A 2001 report by the Science Advisory Board of the FDA specifically focused on the role of Science in the regulatory process at CDRH and serves as a benchmark for the performance of CDRH during that time. The report was comprehensive in scope and called for a number of changes in CDRH. Of particular importance was that 14 recommendations were made (see below). The recommendations dealt with all aspects involving the organization, management and conduct of science in the Center. At the request of our subgroup, CDRH reviewed the status of the 14 recommendations made in the 2001 report and provided an updated response. The response demonstrated that:

- CDRH is motivated to be responsive to constructive criticisms and can make substantive efforts to respond to recommendations.
- Progress has been made by CDRH over the past five years in improving its science infrastructure and management structure/processes.

Examples of some of the important accomplishments have been:

- Introduction of a Science Prioritization Process in selecting research projects
- Emerging Medical Device Technologies Forecasting to help in science prioritization decisions
- Introduction of the Total product Life Cycle (TPLC) concept
- Tracking of publications and presentations of the Office of Science and Engineering Labs (OSEL) as part of the process of accountability for work
- An Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD) combining three key regulatory programs (pre-market review, compliance, and post-market safety monitoring) in a single unit organized as a pilot program
- Medical Device User Fee Modernization Act (MDUFMA) Implementation
- Consolidation of Radiation Programs
- Third Party Review Programs for 510K submissions
- Establishment of The Office of Science and Engineering Laboratories (OSEL), formerly the Office of Science and Technology (OST)
- OSEL appointment of senior staff members as liaisons to pre- and post-market functions of the Center
- A CDRH Communication Improvement Steering Program
- Expanded Consumer Outreach Programs
- Some efforts to increase intra-Agency and extra-Agency collaborations
- The establishment of the Office of Combination Products (OCP)
- The initiation of a New Office of Device Evaluation quality review program for pre-market submissions

6. Recommendations of the 2001 Committee on Science and CDRH

1. CDRH needs to communicate, both internally and externally, a clear vision of the fundamental role of science in the regulatory process. This vision should define the role of science in developing relevant guidance documents and in developing, modifying, and approving appropriate standards. The vision should delineate the role of science in determining how effectively CDRH responds to new technologies and facilitates the introduction of those technologies to users in a safe and effective manner. Development of a system for summarizing the scientific and other factors leading to guidances or approvals (or rejections) would be useful both for FDA, as it reviews its decisions, and for the public.
2. So that science can play this fundamental role, CDRH needs to rethink how it carries out its mission and prioritizes its activities, outsourcing those functions it can while still maintaining oversight, and reallocating its resources so as to expand its investment in science, in all Offices. As part of this rethinking, CDRH should examine its existing organizational structure as well as other regulatory models, with consideration for change to implement and support the TPLC concept. Given fixed budgetary constraints, one model would be for FDA to focus its in-house expertise on selected tasks, and delegate others to official notified bodies or similar entities that derive funding from non-governmental sources.
3. As part of its restructuring of activities to enhance the fundamental role of science, CDRH should assess and reconsider the structure of OST to focus on emerging science and technology; this assessment likely will require a separate review of OST.
4. CDRH should develop a plan for enhancing cross-office and inter-Agency (e.g., FTC, FCC) communication and collaboration.
5. CDRH should establish an electronic database for liaison functions and internal and external expertise inventory.
6. CDRH should develop and implement a formal process for capturing institutional knowledge through more time spent on guidance documents, standards, other written publications, and archiving and retrieval systems, with written precedent files so that when a decision is reached it does not only remain in the "mind" of the reviewer.
7. In recognition of the large staff turnover anticipated in the next five years and in order to fill gaps in scientific expertise, CDRH should expeditiously perform an assessment of the current level and breadth of expertise and use this to develop a long-term strategic staffing and recruitment plan. Major gaps in expertise

should be identified and filled during recruiting for staff replacements due to attrition and turnover. For each position, the options of full-time, part-time, or contract (external) personnel should be considered.

8. CDRH needs to develop procedures and implement staff development/training opportunities to ensure that reviewer mandates for such issues as sample size or randomized trials are shaped by realistic clinical perspectives and relevant ethical considerations.
9. In recognition of its staff being its greatest resource, CDRH needs to streamline processes that encourage scientific growth within the staff and the maintenance of scientific expertise; these processes need to provide for a more inviting career path and a reward structure for scientific personnel, and will require a reallocation of budget resources so that stated goals of staff growth can occur.
10. CDRH should encourage and facilitate the use of internal but non-ODE expertise and also external expertise, including the development of operational and budget policies that promote a more liberal use of external experts.
11. CDRH should expand its outreach to and scientific interactions with industry and universities through visitor programs and the creation of appropriate forums for professional development and for information exchange between FDA staff, industry, and academia, with particular emphasis on new scientific fields that may result in new medical devices within the next five years.
12. CDRH should develop a plan in collaboration with other Centers for the evaluation of combination products. This plan may require changes in organizational structure and operational procedures. Whether it is a new structure or some amalgamation of existing structure, the regulation of these products requires an approach that is least burdensome and embodies the philosophy of CDRH.
13. CDRH should develop and implement a quality evaluation and improvement program. The evaluation system should develop metrics for the assessment of quality as well as the timeliness of results. The focus of these activities should be to achieve high-quality product reviews in a timely manner. Management should implement a system for recognizing, rewarding, and encouraging high-quality product reviews and investigations.
14. CDRH should implement a quality system with continuous evaluation and improvement programs in accordance with ISO 9000 or other relevant standards. The focus should be on CDRH as an organization with a specific mission and on the development of activities that contribute to high-quality decisions that make the most productive use of resources and with a high degree of consistency.

7. Critical Path Initiatives

In addition, CDRH has participated in FDA's Critical Path Initiative. As reported by CDRH (Appendix 2), CDRH's focus has been in pursuing research to further the availability of innovative medical devices, particularly for areas of unmet clinical needs, such as pediatrics. Some examples given:

- CDRH is developing anatomically and physiologically accurate adult and pediatric virtual circulatory systems that could quantify the load and stress forces that cardiovascular and peripheral vascular stent devices can withstand. These models will help assess the safety and effectiveness of new stent designs prior to fabrication, physical testing, animal testing and human trials.
- Developing clinically relevant animal models to improve prediction of toxic effects of medical products on injured tissues in critically ill patients
- Working with industry and the clinical community to develop a new statistical model for predicting the effectiveness of implanted cardiac stents, to measure and improve the long-term safety of these products

Despite the progress, there are continued challenges confronting CDRH that may hinder its effectiveness, now and in the future. The areas of concern can be broadly viewed as follows:

- There remains a continued need for CDRH to clearly communicate a clear vision regarding the role and importance of science in the regulatory progress to all stakeholders.
- While CDRH understands that many new important technologies are now emerging, it is not adequately equipped to understand the science of these technologies. Expansion of capacity to study and understand research areas such as Nanotechnology, Medical imaging, Tissue Engineering, and other rapidly evolving technologies needs to occur.
- There remains a continued need for CDRH to review its methods for prioritizing its scientific activities. In particular CDRH must expand its use of outside individuals for performance of scientific reviews, visiting scientists in residence, and outside reviews of CDRH's science projects as part of its Science Prioritization process.
- There remains a need for increased cross-Agency and inter-Agency alliances and efforts. Cross-Agency efforts must be increased to determine best (and non-best) practices. Inter-Agency alliances with intramural research programs and extramural research can aid CDRH in its research mission.

- Staff Development continues to be an issue of concern at CDRH. Attendance at scientific meetings to understand new technology, and to present scientific research to colleagues appears to be hindered. The performance evaluation process for scientists pursuing research appears to be underdeveloped. However, a new performance evaluation system is being implemented at CDRH.

8. Filling the Gaps and Recommended Approaches

A. Findings

As stated earlier, a comprehensive 10-year CDRH technology forecast has been prepared with the following noted as being 'key' for the future.

- Aging-related devices
- Artificial organs and organ assists
- Computerized devices and intelligent systems
- Early diagnosis/detection technologies
- Genomics, proteomics, metabolomics, epigenomics
- Home- and self-care devices
- Imaging systems
- Minimally invasive technologies
- Miniaturization technologies
- Photonic technologies
- Portable and mobile devices
- Robotic devices
- Sensor technologies
- Telemedicine
- Wireless devices and systems

B. Comments and Recommendations

1. Issue: CDRH's preparation to address future technologies

The forecasting performed by CDRH regarding new technologies presents a good attempt at addressing the issue.

Recommendation 1: Regarding CDRH's preparation to address future technologies

It is recommended that further drill-down of specific areas with a focus on the key research directions of these areas described be performed.

Recommendation 2: Regarding CDRH's preparation to address future technologies

It is further recommended that with rapidly changing technologies, forecasting should be performed every three to five years.

2. Issue: CDRH's has inadequate personnel to carry out their ongoing and future Science Program in Support of their Regulatory Mission.

Background: The SPP is a process by which OSEL's research portfolio is prioritized to meet Center's regulatory science needs. This prioritization is based on the evaluation of scientific merit as well as regulatory impact (including public health aspect) of the proposed research. Personnel at CDRH expressed repeatedly that their efforts in adequately addressing short term needs, and opportunities to address long term needs are hampered by a lack of resources.

It was inquired as to the exact level of resources needed to fulfill the mission at CDRH in the scientific area. The following is an assessment presented by the OSEL Director.

- Post-docs (support for 45 post-docs)

Explanations provided by CDRH:

Senior scientists in OSEL/CDRH carry a large workload in terms of providing technical reviews of regulatory submissions, conducting laboratory research, writing scientific publications, leading standards and guidance activities, and training Center's staff. The Center would benefit by providing post-docs support to senior scientists in terms of advancing long term needs of Center priorities. The Center will benefit not only by increasing the productivity of senior staff members' scientific accomplishments, but also by having younger workforce trained in regulatory laboratory science for the future. Another important aspect of this program is that post-docs bring new skills in emerging technologies that often may not exist in-house.

For example:

- Three to five post-docs would be involved in high-priority areas of MEMS and nanotechnology, including the development of physical, chemical, and biological characterization of nanomaterials, and understanding bioeffects of these materials.
- Three to four post-docs would be involved in emerging areas of optics research, including ultrahigh-resolution optical imaging systems (confocal microscopy and optical coherence tomography) to study the fundamental principles, critical parameters, advantages, and limitations for applications to minimally invasive techniques.

- Three to five post-docs would be engaged in medical imaging research, including evaluation methodologies for diagnostic medical imaging systems (mammography and fluoroscopy, computed tomography, nuclear medicine, diagnostic ultrasound, and magnetic resonance imaging), image quality in multidimensional display devices, and multivariate statistical methods for image evaluation.
- Four to six post-docs engaged in the research of software in medical devices including embedded systems, formal methods, advanced verification techniques, software forensics, and software quality assurance (quality management systems, conformity assessment procedures, etc).
- Three to four post-docs to conduct an interconnected program of biocompatibility, toxicity, and biomolecular research toward the development of data on risk assessment, standards development, and characterization of potential adverse effects of medical device materials and chemicals.
- Students (support for 25 students)

Students, while contributing to laboratory research, learn an important skill in toward their biomedical career aspirations. This level of funding will help us to bring approximately 25 students each year from universities. A steady funding commitment would help maintain continuity of students' engagement with research projects. Bringing summer students, while quite easy to do, does not always produce the optimal outcome. While it is useful largely for the students to have such an experience, the real benefit comes after several months of training and therefore this level of commitment is necessary to fund students at a level of half their time for an entire year.

- \$1M per year for five years for analytical equipment for multi-Center usage, including physical as well as biological analysis of medical device materials, tissues and medical products. Some examples of specialized equipment needs are in x-ray diffraction, optical imaging systems, measurement systems in ultrasound and other imaging modalities, high resolution transmission electron microscopy, etc.
- In the future, in the event that the FDA's field laboratories may not be able to meet testing related to surveillance and import oversight of devices/radiation emitting health products and radiation emitting electronic products, the Center may have to create a new program. Such a program would be required to cover FTE and equipment support.

Comment and Recommendation: Any increased number of fellows should involve a more formalized training program at CDRH. This would include formal mentor–mentee activities, training in the responsible conduct of research, a budget for meeting attendance, and meetings with other post-doctoral fellows to review research directions.

The assessment provided did not include a request for additional scientists, which was surprising (this statement would not be in the report if the previous comment on page 10 is addressed). We suggest the Subcommittee to provide an independent needs assessment. Other scientists individually at OSEL expressed the need for expanding the professional scientific pool of investigators. Additionally, it appears that scientists able to engage in both review and research investigation are becoming scarce, due to their being drawn toward review activities. It was thought by personnel at CDRH that these individuals add a unique perspective and serve an important link between review and scientific research.

Recommendation 3: CDRH’s inadequate personnel levels for ongoing and future science

It is recommended that the personnel requirements provided by the OSEL Director be put in place with metrics determined regarding the ability to address short and long term investigatory needs. A formalized program of training for post-doctoral fellows will be needed to insure they will have an outstanding experience at CDRH. Expansion in the number of fellows should occur only after substantive increases in more scientist personnel (see recommendation below).

Recommendation 4: CDRH’s inadequate personnel levels to carry out ongoing and future science

It is recommended that a program to increase the number of scientists at OSEL labs be designed and put in place. In addition, a program to increase the number of scientists engaged in both review and research investigation pursuits should be put in place. These particular individuals would need to have firm protected time to engage in scientific study.

3. Issue: CDRH Personnel Development: Specifically, the ability of OSEL scientists’ to attend meetings and write papers.

Background: OSEL strives for each scientist to attend at least one professional/scientific society meeting to either present a paper or to participate in a professional development activity. Since 2003, the Center has allocated additional funds for the professional development. In most cases, there is funding available for most staff to attend one meeting per year. Personnel of OSEL expressed the fact that funding for more than

one meeting was difficult and membership in multiple organizations very hard.

Comment and Recommendation: If CDRH is to pursue the best science and assume leadership in science, their scientists must be able to attend meetings and present. In addition, the ability to retain scientists may be dependent upon their ability to feel integrated with the greater scientific community.

Recommendation 5: Regarding CDRH Personnel Development

It is recommended that CDRH provide funding for scientists to regularly attend two meetings per year, and provide a budget for organizational memberships. Reports of activities of CDRH scientists who attend meeting should be reviewed to determine the efficacy of the increase in meeting activities in pursuit of the scientific mission.

4. Issue: How does the science review process at CDRH compare to CDER and CBER? How does staff development compare at CDRH versus CDER and CBER

Comment and Recommendation: The process used by CDRH is unique and other centers in the Agency use different processes. There appears to not be a 'best practices' discussion in this area.

Recommendation 6: Practices of CDRH compare to CDER and CBER

It is recommended that a best practices meeting be held to determine the strengths and weakness of the science review processes of the different centers.

Recommendation 7: Practices of CDRH compare to CDER and CBER

It is recommended that staff professional class development be reviewed to determine hours of class attended by staff, with standard deviations. Best practices in intramural staff development should be adopted FDA-wide.

5. Issue: Involvement of External Scientific Expertise in the Review Process, Scientific Research and Review as part of the Science Prioritization Process.

Background: Limited efforts are currently made to enlist the technical expertise of the outside academic research community. For instance outside senior scientists in residence or other innovative programs have not been considered to bring scientific expertise to CDRH. These types of programs could be particularly advantageous in producing a rapid response scientific team for new technologies. In addition, each year, 8–10 Technical Review Committees are constituted and each committee consists of one faculty member. These committees are constituted as one time events, and dissolved after the meeting. It is believed by CDRH,

that the addition of more than one faculty member to each TRC would place an undue burden on the Agency's compliance with the Federal Advisory Committee Act.

Comment and Recommendation: Greater efforts must be made to harness the expertise of scientists outside CDRH. In addition, the Technical Review Committee structure should be reconsidered. Standing committees for technical review have great merit, since they can provide continuity in the evaluation of projects, and allow for professional development of reviewers. The use of outside faculty members on these committees is important, as they serve as a reality test for the quality of the research using standards outside the Agency. In addition, the faculty reviewers will help the Agency in determining relevancy of work.

Recommendation 8: Involvement of External Scientific Expertise

It is recommended that new programs to engage outside scientific expertise in both review and research be initiated by CDRH.

Recommendation 9: Involvement of External Scientific Expertise

It is recommended that standing committees for technical review be established and that greater numbers of outside faculty be engaged in the process of science review at CDRH.

6. Issue: The fraction of projects motivated by OSEL scientists' on-the-job regulatory experiences – versus those motivated by other factors

Background: In general, almost all research projects are motivated by regulatory experiences, i.e., scientists identify research needs while performing reviews and then develop these needs into proposals while taking input from their counterparts in review offices. An example of exception to this practice is research projects generated on nanotechnology. In this case, since regulatory history of nanotechnology based products is limited, research projects in nanotechnology are based on scientists' understanding of issues the Center will be expected to address in the next few years assuming that our forecast of devices is accurate and nanotechnology-based products will start arriving for approval.

Recommendation 10: Projects motivated by OSEL scientists' on-the-job regulatory experiences

CDRH should begin a program encouraging innovative research addressing future areas of regulatory interest, such as was done

in nanotechnology. This research should result in peer-reviewed publications and should undergo extensive external review.

7. Issue: The percentage of OSEL research proposals that are approved

Background: In the history of the OSEL Science Prioritization Process since 2004, on average 2 projects among approximately 25 are not approved, each year.

Comment and Recommendation: It appears that a 90 percent funding rate for projects may leave little room for new and innovative work.

Recommendation 11: OSEL research proposals that are approved

It is recommended that the criteria for funding proposals at OSEL should be reviewed and a plan for bringing new and innovative research work into OSEL should be developed.

8. Issue: How does OSEL get started in new technical areas? How does OSEL decide what to explore? Where do the startup resources come from? How is the expertise obtained?

Background: Review of scientific/regulatory literature, technology forecast, contact with other agencies, and IDE and Pre-IDE meetings with industry are some of the sources from which OSEL scientists as well as review staff come to know of new technology trends and devices in the horizon. In the past, the Center and OSEL have addressed new technologies such as robotics, organ replacements and assists, wireless systems, combination products, computer-related technologies, minimally invasive technologies etc. Typically, there are no new resources that flow into OSEL to start new projects.

Comment and Recommendation: It will be important that CDRH be nimble in science, and be able to work on the development of new, important projects critical to its mission.

Recommendation 12: Regarding OSEL startup in new technical areas

It is recommended that a separate funding pool be created to support new and innovative research projects. This would be done in conjunction with a reassessment of funding criteria for existing projects.

9. Issue: How does OSEL deal with combination products?

Background: OSEL deals with combination products in the same manner as it does with other products. In the sense that OSEL performs reviews for CDRH and for all other centers in FDA at

their request on specific issues. For example, in the particular case of a drug coated stent product, OSEL worked with CDRH as well as CDER review staff to perform specific reviews.

Comment and Recommendation: As combination products become ever increasing, innovative methods to integrate and streamline review processes between Centers will become important.

Recommendation 13: OSEL and combination products

It is recommended that review task teams for common combination products be established between Centers to make the review process more facile.

10. Issue: OSEL partnerships with outside organizations like NSF?

Background: OSEL has established some collaborations with NSF, NIH (medical imaging joint program with NIBIB), NIDRR, TATRC, and others.

Recommendation 14: CDRH’s OSEL outside partnerships

It is recommended that CDRH and OSEL work with NSF and NIH to develop RFAs in regulatory science that serve to advance the mission of CDRH. These projects could focus on obtaining the long-term regulatory research information for products thought to be important over the next 10 years.

11. Issue: How many pre-market submissions does ODE receive in a year? How many reviews does OSEL do in a year? What level of difficulty are these submissions?

Background: The following is data from ODE’s 2004 Annual Report, describing different types of applications completed by ODE over a period of five years. It appears the numbers for 2005–2006 are about the same as 2004. On average, OSEL participates in about 1100 consults per year. There is no one to one correspondence to the number of submissions completed by ODE to the number of OSEL consults. For example, most of 510(k) submissions are evaluated by ODE or OIVD experts, and OSEL may not get involved in their review. In addition, there may be multiple consults for a given PMA. Therefore, number of pre-market submissions is not correlated to the number of OSEL consults.

Major Submissions Completed FY2000–FY2004						
Type of Submission	2000	2001	2002	2003	2004 OIVD/ODE	2004 ODE Only
Original PMAs	42	53	41	31	39	30

Major Submissions Completed FY2000–FY2004						
Type of Submission	2000	2001	2002	2003	2004 OIVD/ODE	2004 ODE Only
PMA Supplements	474	442	533	494	466	424
Original IDEs	320	284	307	246	221	217
IDE Amendments	251	207	251	217	162	162
IDE Supplements	4,335	4,803	4,711	4,424	4348	4336
510(k)s	4,397	4,150	4,376	4,132	3,917	3,376
Original HDE	6	4	6	2	6	6
HDE Supplements	10	11	13	24	23	22
Total	9,835	9,954	10,238	9,570	9,182	8,573

Comment and Recommendations: Numbers of submissions appears to be flat. It would be important to gain further information regarding the level of complexity of OSEL reviews.

Recommendation 15: The numbers and level of difficulty of submissions to CDRH and reviews by OSEL.

It is recommended that a review of the types of OSEL reviews with measurement of complexity be performed. The criteria for complexity can be determined by CDRH. This would be important in determining personnel needs and training requirements in the future.

Genomics

1. Introduction

A primary mission of the FDA is to protect the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices. The application of high-throughput genomic (and other 'omic') technologies has become an integral part of drug discovery and development. The identification of polymorphisms in two (CYP2C9 and VKORC1) genes responsible for a large part of the variability in dose requirement for warfarin therapy; the identification of genetic variations in viral genomes responsible for the development of resistance to specific antiviral drugs; and the accelerated approval of abacavir and subsequent identification of HLA*5701 as a marker to identify patients with the potential for hypersensitivity, are only three examples where genomics is already having an impact in patient care. There are several more examples and, given the drug industry's focus on integration of genomic (as well as other) biomarkers into their development programs, it is reasonable to anticipate that this trend will accelerate over the next several years.

The FDA has recognized the important role of genomics technologies in fulfilling this mission (indicated in part in the identification of genomics as a key opportunity in the 'critical path' to new medical products¹), and has sought to incorporate genomics into the regulatory process. The process of adaptation of DNA technology within the FDA has occurred at several levels including:

- Formation of a Genomics Group
- Identification of lead scientists within a wide spectrum of divisions
- Enhanced technical capacity, through laboratory modernization or technology.

Genomics technologies may be expected to play an ever greater role in drug discovery and development, and also increasingly in drug evaluation. The FDA must therefore maintain and strengthen its capabilities in genomics to ensure safety of foods and drugs. Scientific leadership is critical to keep pace with scientific advances, to recruit and retain qualified staff, and to expand laboratory facilities. There will be new challenges, particularly in the assessment of drug safety before and after approval.

2. Summary of Findings and Recommendations

Finding 1: DNA technology has enjoyed rapid expansion of usage in biologic research, medicine, and drug development. The effective

¹ <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html>

regulation of food and drug safety now requires competency within FDA to match and exceed the applicant's knowledge in DNA applications. The FDA has sought to incorporate genomics into the regulatory process through the formation of a Genomics Group, but personnel with expertise in genomics are distributed throughout the Agency, and participate in activities on an ad hoc basis.

Recommendation 1: It is necessary to formalize the organization of a Genomics Program.

A Genomics Group was formed in the Office of Clinical Pharmacology (OCP) in the Center for Drug Evaluation and Research (CDER) at FDA, with personnel with expertise in genomics from each FDA Center. The group's stated objective is to integrate pharmacogenomics into FDA review practice by offering key scientific expertise, ensuring proper and adept evaluation of genomic data submissions, fostering and teaching pharmacogenomics within the Agency, and collaborating with FDA internal as well as external stakeholders on projects advancing understanding of how to use pharmacogenomic knowledge in drug development and regulation with the goal of providing safe and effective medical products².

Most prominent among the Genomics Group's activities has been the development of a "Guidance for Industry: Pharmacogenomic Data Submissions" to solicit voluntary submissions of genomic information³. Members of the Genomics Group also participate in the Interdisciplinary Pharmacogenomics Review Group (IPRG) that is responsible for the review of these submissions.

The voluntary submission program has been very successful (approximately 40 such submission have been received by the IPRG) and has helped FDA to gain insight into how and to what extent the pharmaceutical industry is integrating genomics and other exploratory biomarkers into their drug development programs. The increase in submissions, combined with the increase in complexity of the data submitted, indicates that over the next two to five years a significant amount of additional workload related to the review of genomic and biomarker data can be expected.

The voluntary submission process has also been useful for identifying gaps in regulation, and has also provided the basis for the development of new guidances, improved review practices, fostering the application of genomics in the clinic, or leading to the re-labeling of existing drug products based on new genomic knowledge. However, the continued absence of an organized structure may lead to difficulties in staff recruitment and retention, since genomics may not be a primary activity for staff members distributed among various divisions.

² 'Pharmacogenomics 2010: Vision and Strategy,' draft document; 2005

³ <http://www.fda.gov/cder/genomics/VGDS.htm>

Finding 2: About 60 full- and part-time employees, from across the FDA, participate in genomics activities, including review⁴. However, there is only a very small core team, with a large number of partially funded staff who have other major responsibilities.

Recommendation 2: Mechanisms for recruitment, training, and retention of high quality scientific staff with multi-disciplinary training and skilled in bioinformatics are needed to support the highly *developed and labor-intensive efforts required for genomics analyses.*

Industry initiatives using genomics deserve FDA study as part of its role of overseeing safety of clinical trial drugs. It cannot be predicted at this time how well these new safety technologies will perform in reducing toxic risk in man. Such evaluation could require either a retrospective examination of failed and successful (safety) Phase I/II compounds, approved and failed drugs (safety) in Phase III. Another strategy would examine past approved drugs with and without black box labels. The FDA should lead the consideration of the scope, cost, and ownership of such studies, and must be properly staffed and adequately funded to do so.

The committee recommends an increase in staffing expertise to be able to exploit genomics to fulfill this mission. Up to 80 FTEs will be needed to monitor safety in areas such as preclinical technology, clinical stratification, biomarker evaluation, post-clinical technology; and food safety.

The Genomics Group has participated in activities within and outside FDA to try to advance genomics technologies. Monthly meetings of genomics and proteomics interest groups for reviewers and non-reviewers have been organized. There have been training programs on experimental design, sample preparation, and data analyses of microarrays. An intranet Web site is planned to make educational materials accessible to everyone at FDA. These educational efforts should be continued.

Finding 3: There is and will continue to be rapid evolution of genomics technologies and statistical methods, requiring continuing training and education of FDA scientists and reviewers. An effective way to leverage FDA resources is through outreach activities with all stakeholders.

Recommendation 3: The committee strongly recommends increased collaboration with academic centers of excellence, other agencies, and the private sector.

There are many benefits from external collaborations — training opportunities for FDA personnel; opportunities to collaborate with other scientists and access to additional research resources; opportunities to participate in the development of industry standards. The FDA has a variety of research collaborations with other federal agencies; for example, to develop microbial forensics tools for the identification of

⁴ Overview of Genomics Resources at FDA, memo, March 13, 2007

pathogens that may be intentionally used to contaminate foods. FDA personnel have participated in various technology-standardization programs, including the Microarray Quality Control Project (MAQC), the External RNA Controls Consortium (ERCC), and the International Conference on Harmonization (ICH). There have been numerous FDA/industrial meetings regarding data sharing of RNA expression data, collaboration with non-profit sequencing organizations (microbial diseases), and approval of DNA diagnostics.

Public/private initiatives could accelerate adoption or rejection of new technologies. More effective, efficient, and less restrictive processes for establishing collaborative agreements with non-federal entities (CRADAs) are needed. A closer working relationship, including joint projects, with the National Institutes of Health or with academic centers of excellence, is strongly encouraged.

Implementation may require innovation in development of outsourcing mechanisms, funding, and governance. The committee recommends up to 10 new CRADAs to add to its ability to oversee critical technologies in safety.

Finding 4: Monitoring drug safety after they are on the market (post-launch safety) is a high-priority issue for the pharmaceutical industry, public, and the FDA. Everyone wants transparency on safety, a better public understanding of risk/benefit, as well as the development of testing approaches to avoid clinical risk by “toxic risk gene” diagnostics. Such diagnostic capacity adds a new direction to safety drug usage. An example of “toxic risk gene” identification was achieved by a study of the hypersensitivity related to the HIV drug, abacavir. The gene for risk was identified by comparison of the genetic differences between affected and unaffected patients. The strategy works, but the efficiency of such success for all Phase IV toxicities is not established.

Recommendation 4: Public/private initiatives will be required for the continuing evaluation of the safety of approved drugs.

Large clinical databases could more rapidly identify an unwanted effect of a drug, and distinguish suspected adverse effects (AEs) that were drug induced disease or occurring by chance. Large cooperative health care systems (Kaiser) have already expressed interest in participating in a clinical database initiative. Such an initiative would employ electronic medical records, AE electronic entry, and algorithm analyses. Expert review of data, full understanding and cooperation of patients for their medical record usage, and confidentiality are required. There is little doubt public/private initiatives will be required in exploring the utility to safety monitoring of large patient cohorts. Clinical sample bio-banking would accelerate such studies.

Finding 5: The recruitment and retention of personnel expert in genomics is simply a first step. In order to fully develop a program that

integrates genomics and other developing technologies within the Agency, the FDA must develop in-house expertise.

Recommendation 5: Within the FDA, there should be a genomics central lab, with expertise in expression profiling, sequencing, informatics, proteomics, metabolomics, and systems biology.

The establishment of an FDA Genomics core with expertise in expression profiling, sequencing, informatics, proteomics, metabolomics, and systems biology) will require dedicated space at the White Oak facility as well as adequate staff. Some of the 80 FTEs recommended for genomics should be allocated for laboratory personnel and support staff, possibly funded by CRADAs. These experts may also be outsourced. There should be clear lines of assignment and reporting of projects from the central lab. At least initially it would be advisable to establish strong partnerships with academic centers of excellence to facilitate jump starting the core and also to enhance the chances of recruiting the strongest scientists into the Agency over time.

Recommendation 6: In order for the genomics core group to function effectively, it is critical to upgrade FDA's information technology infrastructure.

The FDA must implement the real-time acquisition and sharing of genomics data. Incorporating genomics technologies into FDA review pre- and post-marketing will generate large datasets, requiring the development of data storage, mining, analysis and risk evaluation tools; and an aggregate knowledge base to allow FDA scientists to interpret and evaluate data from high-throughput technologies. As a fast-developing field, genomics is still developing commonly accepted standards for complex datasets. The FDA must participate in these standardization activities — involvement is an opportunity to guide future submissions. Specific recommendations for IT infrastructure to support the core and other areas of emerging science are discussed in the report of the IT subgroup in Appendix K.

Surveillance/Statistics

1. Summary of Findings and Recommendations

A. Resources

Extensive new resources will be needed to bring the surveillance programs in particular to where they need to be. (Statistics needs more resources also, but the surveillance needs for access to external databases will be particularly costly.) Peter Hutt has prepared a document that provides more detailed justification for specific amounts of additional resources than has been put forward anywhere, including the IOM report. This should be a valuable contribution to any efforts to support budget increases of a certain magnitude.

B. Databases

The surveillance programs need access to more and better data than they have now. For the medical product centers, possible resources could be HMOs, CMS and the VA. In addition to funds to gain access to these data sources, FDA will need increased scientific and informatics staff to use the data efficiently and effectively. The surveillance groups in CVM and CFSAN also require additional data sources and the staff to fully utilize them.

C. Collaborations with external experts

In order to achieve additional capacity in the areas of statistics and surveillance, the FDA needs to have mechanisms for developing sustained collaborations with external scientists as new scientific issues emerge. FDA will not be able to effectively maintain all the scientific expertise it needs within realistic budget expectations. The academic community nationally, together with scientists in other health-related government agencies, represents an enormous potential source of expertise that can be engaged to address issues of relevance to both drug safety and efficacy evaluation and for addressing the issues of human capital.

Studies of drug mechanism need to be integrated with the collection of data from clinical trials and surveillance programs to inform and to facilitate rapid and accurate assessments of potential safety concerns.

Capability of rapidly mobilizing an expert task force to deal with an emerging acute problem should be developed. Such a task force might involve external scientists — a sort of “National Guard” for product safety issues.

Given the trajectory of “megatrends” – globalization of drug development, increasing volume of products under development,

rapidly changing science, aging population requiring increasing exposure to medical treatments for chronic diseases, genomics and personalized medicine — it is naive to think the FDA will be able to keep up without creating a fundamentally different personnel policy. These trends will amplify the data/analytic needs on a huge scale.

D. Workforce

A high priority for the FDA should be to attract a core of very talented biomedical scientists who can administer an increasingly complex and collaborative science base, with much expertise likely leveraged from external organizations such as universities, other science agencies and research institutes. There is a need for mechanisms to incorporate the world of expert talent for highly specialized analysis and science while keeping decision making internal to FDA.

E. Training and Professional Development

Training in the sorts of interdisciplinary issues needed to make good regulatory decisions is essential. Development of such training must involve both FDA and external scientists. FDA staff needs broader, interdisciplinary training, and external scientists studying regulated products need to understand the application of current science to decision-making in the regulatory setting.

A practical matter that must be resolved is the growing set of disincentives for FDA staff to be publicly engaged in the scientific enterprise. We are all dismayed by reports that FDA scientists are finding it more difficult to get permission to be involved in collaborative publications with outside colleagues, and that funding to attend meetings of professional societies is being restricted when a scientist has a leadership role in the society. These policies are not only demoralizing to current staff, they will also reduce FDA's ability to recruit highly qualified scientific staff in the future.

2. Current State Findings and Recommendations

A. Science Mission Overall

HHS and Congress must realize that the FDA must have a strong science base in order to improve its capability to effectively communicate science related to risks and benefits. In particular, there is a need to develop increased awareness of and expertise in design and analytical methods in emerging areas such as Bayesian methods, bio-imaging, genomics, adaptive and targeted designs, and an evaluation of current and developing approaches to design and analysis. In addition, there is a need for the evaluation of current surveillance approaches.

Recommendations: The committee offers these recommendations to address the overall science mission.

- Develop quantitative approaches to balancing risks and benefits that can be used broadly to assess new products.
- Increase expertise in scientifically based risk communication strategies.
- Develop and provide regular interdisciplinary training to senior scientific staff in areas of emerging science to optimize regulatory decision-making.
- Consider ways to measure and disseminate information on benefits in real-world settings.
- Develop and evaluate study designs for targeted therapies that may facilitate move toward personalized drug treatment.
- Expand the drug safety framework to apply “active surveillance” to medical devices and animal drugs and even possibly foods.
- Increase involvement of external stakeholders in evaluation of FDA approaches and processes.

B. Science Infrastructure

1.) Scientific Expertise

Key Findings

In order to address emerging issues, FDA science capacity needs significant strengthening, both with in-house scientists and enhanced access to wider scientific community. The FDA needs an increase in the physician workforce that can direct and evaluate studies relevant to surveillance. Additional funding is needed specifically for methods development.

Recommendations

The committee offers the following recommendations:

- Establish ongoing, sustained programs of scientific exchanges between FDA and academia/other scientific organizations.
- Make increased use of advisory committee scientists in areas where in-house expertise is limited.
- Integrate NCTR statistics group with those of other Centers.
- Increase participation in CDC’s Epidemic Intelligence Service to provide training in regulatory science and develop future FDA leadership.
- Consider merits of establishing FDA-specific training and/or exchange programs.

2.) *Professional Development*

Key Findings

There is a need to increase opportunities and expectations for FDA scientists to enhance their skills along with the establishment of expectations that they do so. The restoration of an encouraging atmosphere and support for attendance at professional society meetings as well as the removal of barriers to participation in leadership roles in professional societies will support this.

Recommendations

The committee offers the following recommendations:

- Allocate resources to support training.
- Change policies and resources to encourage participation in professional societies.
- Increase personnel sufficient to allow all scientists some time to pursue research.

3.) *Priority Setting*

Key Findings

Strategic planning regarding scientific issues is key to setting priorities and is more effective if the planning process includes both external and internal stakeholders.

Recommendations

The committee offers the following recommendations:

- Conduct evaluations of current surveillance processes; involve external experts as well as internal stakeholders.
- Conduct cross-Center strategic planning in both stats and surveillance, with input from academic advisors (advisory committee members, other SGEs) and expert colleagues in other agencies (e.g., CDC for surveillance, NIH for new statistical methods).

4.) *Resources and Technology*

Key Findings

Resources and technology play prominent roles in the surveillance responsibilities. There is a great need for increased access to existing data that could permit more rapid and reliable assessment of safety concerns. Increased informatics support is required to permit efficient use of data resources and to study the potential of information available from electronic medical records. In addition there are needs

for unique device identifiers, estimates of baseline rates to help interpret reports submitted to passive surveillance systems, and the capability of utilizing data from archived submissions to enhance insight into emerging and/or potential safety issues including increased attention to surveillance systems for food safety (both for humans and animals). There should be a move to all-electronic reporting and participation in standards development.

Statisticians need to increasingly be involved in safety assessments.

Recommendations

The committee offers the following recommendations:

- Develop plans for more active surveillance system(s).
- Evaluate CVM causality assessment system.
- Ensure that all surveillance groups have access to existing tools such as data mining software, and are trained in their use.
- Enhance CVM safety data system by gaining access to data from pet hospitals to improve animal drug safety surveillance.
- Use melamine experience to inform planning of improved surveillance system
- Develop partnerships with other funding agencies to support needed post-market studies that can inform public health initiatives.
- Increase informatics staff to ensure full participation in standardization initiatives (i.e., CDISC).
- Establish more realistic budgets to support needed activities, whether via PDUFA or from general revenues.
- Develop archival systems to permit learning from previous applications.

5.) Collaborating/Leveraging

Key Findings

More opportunities for cross-Center interaction are needed to establish best practices and ensure appropriate consistency of approaches. In addition more formal collaborative structures should be established for work with other agencies (e.g., with CDC, CMS and the VA for safety surveillance; NIH, AHRQ and the VA for clinical trial methodology and drug safety), and particular increased attention to surveillance systems for food safety (both for humans and animals). These structures should permit collaboration across all FDA Centers as relevant to avoid development of a "silo" mentality and to increase regulatory consistency with regard to study design issues and statistical approaches more generally. Increased opportunities for in-depth

scientific interactions with academic researchers, such as might be achieved with visiting fellowships, IPAs, etc., would benefit both the FDA and the external scientific community.

Recommendations

The committee offers the following recommendations:

- Surveillance
 - Establish ties with extramural scientists with expertise in drug mechanisms and pharmacogenomics to better integrate such knowledge into safety surveillance activities.
 - Improve collaborative structures for working with other agencies within HHS (CDC, NIH, AHRQ [CERTS]) as well as other relevant federal agencies (USDA, DHS, DVA).
- Statistics
 - Consider development of a grants program, preferably in partnership with the NIH, to support and inform methods for solving emerging problems facing FDA
- Surveillance and Statistics
 - Organize scientific conferences to better educate outside scientists about FDA practices, procedures, policies, and to promote use of consistent approaches across FDA units.
 - Develop public-private partnerships for safety surveillance that may enhance FDA's ability to make sound judgments on safety signals and alerts.
 - Establish Inter-Agency work group on roles and responsibilities for Food surveillance.
 - Consider changes to regulations requiring manufacturer reporting for animal food and drugs.
 - Evaluate potential enhancement of global networks established for disease and weather tracking to permit tracking of food-borne outbreaks.

C. Critical-Path Approaches

Critical Path Initiatives are needed for both surveillance and statistics, but additional resources are required for progress.

- Reconsider priorities on regular basis.
- Consider whether additional partnerships would be useful.
- Establish timeline for regular evaluation of Critical Path activities.
- Conduct strategic planning for research.

D. Management Structure/Processes

1.) *Integration into Core Regulatory Activities vs. ad hoc Activities*

Key Findings

Appropriate and clear expectations for scientific staff in terms of activities focused on generalizable science rather than specific regulatory tasks should be established.

Recommendations

Consider options, such as establishing an FDA “research center” where FDA staff could spend “sabbatical” time.

2.) *Overall Direction Setting and Planning*

Key Findings

Planning for the expected wave of retirements over the next few years is critical. Management should develop an understanding of the reasons for turnover; in particular, why it is higher in some areas. Surveillance programs, particularly for CDER, will likely need to adjust the mix of disciplines (more MDs) in future staffing.

Recommendations

Develop more pro-active recruitment program for statistical scientists and pharmaco-epidemiologists.

3.) *Program Assessment*

Key Findings

External evaluation of scientific programs (regulatory science as well as basic science) should be conducted.

Recommendations

- Utilize advisory committee members with relevant expertise to conduct “site visits” of FDA divisions with science-based responsibilities.
- Establish “Board of Scientific Advisors” for statistics programs and surveillance programs FDA-wide, to avoid unjustifiable inconsistencies and to optimize internal leveraging of expertise.

4.) *Overall Program Management*

Key Findings

Managers must be able to support their staff's, engagement with the broader scientific community. FDA must seek out managers with strong scientific qualifications who can successfully implement strategies of increased engagement with outside scientific community and oversee outsourced research.

Recommendations

- Encourage FDA scientists' participation in professional society activities and remove obstacles to Agency scientists taking leadership roles.
- Publicize available scientific openings more heavily; consider announcing multiple positions simultaneously to garner maximal attention.

Information Technology (IT)

1. IT Critical Facts

Investment in information technology at the FDA is critical to enable the FDA to fulfill its regulatory mandate. Importantly, there is strong evidence that the FDA is capable of effectively leveraging significant new investment.

While the Subcommittee discovered and enumerated numerous critical deficiencies in information technology at the FDA, the Subcommittee believes that there is strong evidence of important, but too slow, progress over the past few years. Significant investment in IT is warranted and should yield productive results because:

- New CIO, CO, and CTO with strong track record at other government agencies
- Internal IT governance boards are operational with strong program/scientific support and participation
- IT activities are evolving into more efficient centralized administration
- Standards activities are in process with strong external collaboration
- Recognition of key challenges is consistent across large groups of internal FDA stakeholders
- Business process delineation is progressing well
- Strong collaborations with external partners
- The Office of the CIO is championing five critical initiatives

Critical information technology deficiencies at the FDA include:

1. The FDA technology infrastructure is outdated and unstable with 80 percent of network servers greater than five years old which is beyond the recommended life of the machine.
2. There is no continuity of operations or disaster recovery plan.
3. Electronic submissions are only at 40 percent.
4. There is a lack of sufficient standards defined for all aspects of data exchange with the FDA.
5. There is a lack of legislative mandates to support the FDA's role in establishing data standards for electronic data exchange, as well the lack of mandates that submissions must be electronic.

6. The recommendations of the Task Force on Counterfeit Drugs that have been issued and iterated in 2004, 2005, and 2006 for electronic supply chain documentation (e-pedigree) are hardly progressing.
7. Food and Drug Administration Accountability Act (FDAAA) Title IX legislation has passed the Senate and is pending in the House mandates creation of pharmacovigilance networks, but does not mandate clinical trial networks or hybrid clinical trial/pharmacovigilance networks.
 - Mandates access to 25 million patients by 2009 and 100 million patients by 2012, but does not take into account the diverse patient cohorts that may be needed for many drugs.
 - Fails to recognize the complexity of that mandate in light of less than successful attempts to establish large Biosurveillance projects over the past five years as well as the failed attempts to progress the anti-counterfeit drug initiatives.
8. The FDA and other stakeholders are not capable of remote monitoring or sensing for contaminants at manufacturing sites, in transport environments/vehicles, or at any point in the regulated product supply chain. Given that only approximately 1 percent of food is inspected at ports and sampling of manufacturing sites is also very low, this type of automation will be emerging as the only feasible method to credible monitoring of our food and regulated product supply chains. It is not reasonable to expect sophisticated sampling methodology, as is proposed, to protect the public's health when a very small sample is taken.
9. The FDA has warehouses full of clinical trial data that is all paper-based and not readily available for analysis.
10. There is still an inability to collect, store and mine clinical trial data in electronic format.
11. Emerging science and risks are not adequately supported by IT and require special IT initiatives to build scientific/technology capacity to effectively regulate related products for efficacy and safety. The FDA cannot credibly manage the data to regulate panomic products, wireless health care devices, nanotechnology products, and medical imaging products because they cannot acquire and keep pace with the rate of innovation in these areas.
12. At approximately \$200 million, the FDA IT budget is only 40 percent of the CDC's approximately \$500 million IT budget, though its mission, e.g., regulating \$1 trillion of consumer goods, seems at least as large in scope.

2. Overall Finding

Based on the findings of the IT working subgroup, it is clear that the information infrastructure and IT staffing do not sufficiently support current regulatory scientific or operational needs and require urgent and significant evolution to meet emerging needs.

3. Overall Recommendation

The FDA must develop and execute a comprehensive IT modernization plan that is driven by the regulatory mission and based on best IT practices that addresses the immediate regulatory science and services needs of the Agency as well as the rapidly emerging IT needs required to support new technologies, scientific methodologies, products, and global business activities.

4. Information Technology Overview

There is strong consensus among all subgroups of the overall working group that information technology is a critical enabler for successful regulatory science and regulatory services at the FDA. While it is clear that FDA scientists must have access to appropriate information to fulfill its public health mission, the term information technology has different meanings to different people. Any discussion of the IT environment at the FDA must first clarify the definition of IT, specific functions of interest, and scope of implementation.

A. What is Information Technology?

For the purposes of this report, the scope of information technology is defined broadly to include:

- All data and information assets, e.g., databases, reports
- Data and information collection, management, and sharing initiatives and networks
- The information technology infrastructure including hardware, software and telecommunications
- Information, computer, informatics sciences and related disciplines
- All associated IT management and planning activities such as information security, capital planning/investment control and enterprise architecture

Standard IT terminology phrases “enterprise architecture” or the “enterprise” are used throughout this report. The word “enterprise” simply refers to the entire institution, in this case, the FDA. This is a critical concept because enterprise-level management of IT is critical to ensure efficient, cost-effective purchasing, maintenance, etc.

While the above defines information technology for the purposes of this report, the specific functions/services that are delivered through IT are enumerated immediately below.

B. What FDA Functions Are Supported by IT?

The FDA IT-related functions and activities include, but are not limited to, the following:

- Electronic application processing
 - Submissions
 - Ongoing communications
- Safety and efficacy data sharing networks that include clinical trial and pharmacovigilance support
 - Medical product (e.g., prescription drugs, biologics, devices) information infrastructure/data sharing networks
 - Pre-market clinical trial information infrastructures
 - Post-market adverse event information infrastructures
 - Integrated pre-market and post-market information infrastructures/networks
 - Non-medical device adverse event networks, e.g., food, cosmetics, radiation emitting devices
- Risk detection and sensing to facilitate quality activities. Sensors that may be deployed in various environments to monitor contamination (intentional or unintentional) and quality. Deployment of these sensors will likely be the only method for overcoming the increasing burden of inspection of FDA regulated products.
 - Train cars that transport food are regulated by FDA to ensure absence of contamination of the car that may impact food quality
 - Manufacturing sites for quality, contamination, and supply chain verification
 - Automation of food supply monitoring by sensor placement to augment the very low and inadequate sampling rate (approximately 1 percent) of all imported food
- IT support for the scientific activities
 - The basic technology infrastructure, the network of desktop computers and servers including telecommunications
 - Data archiving and mining
 - Analytics including statistics
 - Modeling
 - Segregated networks to support specific laboratory needs

- Support of the emerging sciences and risks (enumerated below)
- Collaboration platforms
 - Email
 - Collaboration portals
- Policy, guidelines, and legislative mandates for IT
- Establish data standards
- Requirements for automation
 - Application submissions
 - Anti-prescription drug counterfeiting activities, e.g., RFID or visual scanning
 - Automated sensing for contamination or composition
- IT expertise to regulate certain technology-based products including, but not limited to, the following:
 - Cardiovascular and cardiorespiratory monitoring devices
 - Central nervous system monitoring devices
 - Clinical chemistry monitoring devices

C. What is the Geographic or Operational Scope of IT Under Discussion?

IT requirements and implementation realities vary greatly for infrastructure efforts that are constrained to FDA environments versus efforts that include environments of other stakeholders. For example, it is more straightforward for the FDA to modernize its own network infrastructure or to improve its data archiving/retrieval capability because it controls planning, investment and execution. Similarly, the FDA should be able to mandate and establish an effective electronic submission/communication platform for all Investigational New Drugs (INDs), New Drug Applications (NDAs) and Biological License Applications (BLAs) because it can create this infrastructure as part of its own internally controlled technology environment.

However, it is much more complex for the FDA to influence or establish national or international data sharing networks that involve numerous stakeholders and infrastructure that it does not control or manage. Examples of this include the evolving large national health information exchanges and the evolving national health information network, as well as the FDA's recommended (Task Force for Counterfeit Drugs – 2004) RFID-enabled e-pedigrees for drugs.

It is a dangerous but common mistake to underestimate the complexity of establishing information infrastructures that must exist and function across infrastructure owned and operated by diverse

stakeholders. The FDA must be able to make critical investments in extramural information infrastructures and information sciences. These efforts will catalyze the successful development and, ultimately, sustainable operation of these networks because they are the future foundation for pre-market and post-market evaluation activities.

5. FDA Key Challenges that Impact IT

Ongoing challenges confronting the FDA in the technology arena can be stratified into these broad areas:

- Processing vast amounts of data and information requires state-of-the-art business process development, technology infrastructure, human resource capability and information processing capability.
- New science and new public health risks require new expertise and infrastructure capability, without which the FDA is not capable of protecting the health and well being of the public.
 - Pan-omics
 - Wireless healthcare
 - Nanotechnology
 - Medical imaging
 - Telemedicine platforms
 - Electronic health records, especially as they interface with medical devices
 - Bioterrorism
 - Rapidly increasing number of imported products
- Complexities that arise from shared, overlapping or intersection responsibilities with other federal agencies:
 - Food safety
 - Imported products
 - Pesticides
- Rapidly evolving technology:
 - Technology evolves a magnitude approximately every three and a half years
 - Rate of progress/innovation is accelerating
- Increasing oversight and expectation for the FDA:
 - Consumer groups and advocates want drugs to reach the market more rapidly, while the challenges of regulation increase

- Industry would like more efficient submission and review processes
- The public wants risks associated with food/drugs/devices to approach “zero”
- Rapid growth of imports
- Rapid growth of manufacturing sites both domestically and internationally

6. Specific Findings and Recommendations

While, as noted above, the FDA is making important changes and progress in the IT arena, the FDA also recognizes and has clearly communicated many of its IT challenges with the IT subgroup. This section outlines specific findings or challenges in the IT arena and proposes a set of recommendations to mitigate each of the findings.

Finding 1: Quality, Safety and Efficacy: Critical Information Supply Chains

The FDA’s current critical information supply chains are, at best, inefficient, cost intensive, prone to errors, result inability to access data and thus missed opportunities to both innovate and identify risk all of which adversely impacts on the FDA mission to improve and protect the health of the public. Furthermore, processes for data and information exchange, both internally as well as among external partners, lack clear business processes, information technology standards, sufficient workforce expertise, and a robust technology platform such that the FDA can’t credibly process, manage, protect, access, analyze and leverage the vast amounts of data that it is processing.

The core supply chains and/or components include but are not limited to:

- Pre-market activities for food, drugs and medical devices, and radiation emitting devices
- Post-market surveillance activities food, drugs and medical devices, and radiation emitting devices
- There is insufficient clarity around data needs, standards, and information flow in domains where multiple agencies share related regulatory responsibility. These issues may result poor data and information, redundant resource utilization, and missed opportunities for collaboration that in aggregate adversely impact on the FDA’s ability to efficiently and effectively protect the nation’s people. Examples include (1) food which in various circumstances would involve FDA, CDC, USDA, and the Department of Agriculture; (2) pesticide regulation that might include FDA and EPA; (3) herbicides, which is usually EPA, but

requires essentially the same approach as pesticide regulation from an IT perspective; and (4) imported products that may involve all of the above in addition to Customs and Border Control, DHS.

- Quality control activities
- Labeling
- Listings and registration

Recommendation 1: Critical Information Supply Chains

- Develop and implement an enterprise approach to the processing of all types of FDA submissions
- Develop and implement an enterprise approach to post-market pharmacovigilance activities
- Provide leadership and participate in the development of standardized approaches to facility listings and registration activities
- Identify and leverage emerging data and information assets such as large repositories of clinical data due to implementations of electronic health records at large provider networks or payers.
- Develop partnerships to accelerate the development and implementation of automated sensing and monitoring capability at manufacturing sites to decrease the burden on field teams and improve the quality efforts of the FDA
- The FDA should support legislative activities to establish critical information technology standards. These standards will not only improve work flow among stakeholders but will ensure that policy and science decisions are based on the best information possible. While the federal government may be hesitant to impose information technology standards, the FDA's specific regulatory mission is dependent on accurate, reliable, secure, and durable data in order to achieve its mission to protect the health and well being of the public. These standards should include all aspects of data and information exchange.
- An information security and continuity of operations plan should be developed, tested and iterated
- Establish cross-Agency collaborations to create clear information supply chains including clear business process mapping, description of roles and responsibilities, data/information standards, and data/information flows

Finding 2: New Science and Emerging Risks

The FDA's information infrastructure is not capable of responding to new and rapidly evolving requirements that are arising from 'new science' and new technologies.

Recommendation 2: Science and Emerging Risks

- The FDA should ensure that informatics/IT expertise is represented on the FDA Science Advisory Board.
- The FDA should establish an ongoing informatics/IT advisory working group that consists of both public and private members and that reports up to the FDA Science Advisory Board. The purpose of this working group is to leverage resources external to the FDA to improve innovation and to identify emerging needs/risks, while at the same time helping to ensure the FDA and its stakeholders are
- The FDA should have a clear information technology adoption plan that synchronizes with current and projected regulatory science needs with a time horizon of at least three years.
- The FDA should identify areas of unique and critical mission that might present the FDA with an opportunity for leadership and innovation in the information technology arena. One example might be the need to establish a National Biomarker Repository.
- While there are several examples of 'new science' and emerging risks they all share a common theme. Specifically, there is a need for the FDA to establish a process of innovation that enables it to: (1) identify emerging science, technology and public health risks, (2) leverage science and technology experts to determine how current processes, platforms, tools, data, and information networks may change, and (3) develop and implement effective response so that the promise of 'new science' and technology is transformed into productive innovation rather than disruptive risk.
- The FDA should dedicate IT resources to specifically address the information science and infrastructure needs of the new sciences. Ideally, these resources would be dedicated to the IIRISC activity previously described if, and when, the FDA establishes this activity.

Finding 3: Food Safety

The challenge of protecting the nation's food supply presents a useful and important case study as it highlights the serious deficiencies that exist in the networks for surveillance, investigation, and quality of FDA regulated products. The risks that globalization present are also evident as the volume of food, the diversity of sources and the sheer quantity of sources renders surveillance of imported food products an extraordinary challenge that starves for technology support. As has

been highlighted above, panomics has presented both challenges and rewards with respect to the FDA mission. In the case of the protection of the nation's food supply, panomics has revolutionized the strategy for tracking sources of and spread of food-borne outbreaks as exemplified by the CDC's PulseNet activity.

The FDA has a mandate to regulate approximately 80 percent of the food consumed in this country. To effectively fulfill this mandate, the FDA must:

- Be able to monitor quality/contamination at points of production, transportation, entry into the country and sale
- Participate in and support investigations of outbreaks of contaminated food in a timely fashion

Recommendations 3: Food Safety

- Establish food surveillance at all ports of entry by leveraging technology for automated sensing for quality and contamination
- Establish ability to monitor quality/contamination at points of production, transportation, entry into the country and sale
- Establish effective coordination of food safety activities across all government agencies with food-related regulatory mandates
- Establish and/or participate in the establishment of national repositories of molecular epidemiology, e.g., PulseNet-like activities, that enable fingerprinting of etiologic agents to identify related outbreaks and sources

Finding 4: Information Technology Platform/Infrastructure

The FDA data and information processes remain at risk due to an incomplete migration to a robust enterprise model. Furthermore, the FDA has vast amounts of data and information that it has collected in paper format that is not easily accessible thus representing missed opportunity for analyses that may yield important insights for products under review or on the market.

The current IT budget is clearly insufficient to support the FDA's mission. For example, more than 80 percent of the FDA network servers are more than five years old and, thus, are in service beyond the recommended life expectancy of such machines. If even such fundamental IT infrastructure components are inadequate, how can the FDA be expected to invest in the capability to manage such emerging risks as the new sciences (panomics, wireless healthcare solutions, nanotechnology, medical imaging), bioterrorism threats, and remote sensing networks to scale the monitoring of manufacturing or prototypes for complex global electronic product code architectures to support anti-fraud activities? As a simple example of the consequences of an unstable technology infrastructure, the FDA's participation in the

national *E. Coli* O157 outbreak in 2006 was hampered by outages in the FDA email system that depends on the outdated FDA technology infrastructure.

The FDA must have a sizable budget to support extramural activities that accelerate the development of health information exchanges to support clinical trials and pharmacovigilance. These entities will be external to the FDA and will be owned by the health care providers and payers. However, it is critical that the FDA establish the necessary data and information standards, as well as consolidated repositories that store data for clinical trials and pharmacovigilance, so that the independent health information exchanges can aggregate data.

Recommendation 4: Information Technology Platform/ Infrastructure

- The FDA should accelerate efforts to migrate its technology platform to a robust enterprise model with state-of-the-art data centers, redundant internet and telecommunications capability, stringent information security protocols, and a robust continuity of operations plan.
- There is a critical need to assess the specialized needs of the laboratory community and to develop appropriate infrastructure that provides FDA laboratories with access to specialized tools without adversely impacting on the general FDA network infrastructure
- Develop a strategy to migrate, to the extent possible, the vast amount of legacy data/information that resides in paper format into digital format. This activity should include the development and implementation of strategies to access and analyze these data.
- FDA internal collaboration portals should be developed to facilitate collaborative activities and innovation
- Establish effective communication strategies, platforms, processes, and content management capability to effectively communicate risk with all appropriate stakeholders
- The FDA must invest in the development of large-scale, sustainable data sharing infrastructures that can support clinical trials and pharmacovigilance, quality activities, registration activities, and manufacturing life-cycle activities, e.g., electronic product coding to prevent manufacturing fraud. These are expensive but critical investments.

Finding 5: Information Technology Best Practices

The FDA does not have effective information technology best practices to support the required information infrastructure, products, and services. The FDA is aware of and working hard to mitigate these

challenges but progress is impeded by legacy culture, need to complete migration to enterprise-level IT management, and insufficient resources to staff the evolution to best practices in a timely manner.

Recommendation 5: Information Technology Best Practices

The FDA needs to accelerate progress on the development and implementation of information technology best practices. Specifically, the Agency needs to rapidly implement:

- A comprehensive IT enterprise management model that is capable of servicing even the most specialized scientific needs.
- Effective IT governance that is tightly coupled to the Agency's regulatory science through the evolving Bioinformatics Board (BIB) and the Business Review Boards (BRBs). The BRBs should have representation that includes science and technology experts who can work with the Office of Planning to develop the required business process mapping that can be leveraged to develop the needed information infrastructure.
- An enterprise architecture that is based on robust business process mapping to ensure effective support all regulatory mission needs
- Capital planning and investment control activity that ensures that funds are appropriately invested and managed. This should include a peer review process consisting of internal and external program stakeholders.
- There should be a clear IT strategic planning process that includes:
 - Clear performance measures for all IT activities from 'best practices' to 'scientific support' to ensure goals and objectives are clearly articulated, achievable, and accomplished.
 - An ongoing process, rather than an event every three to five years, with substantive subject matter expertise ownership and oversight

Finding 6: Information Technology Workforce Improvement

The FDA's information technology workforce is not capable of implementing, managing and innovating a sustainable information infrastructure to support the FDA regulatory mission.

Critical IT programs at the FDA that are responsible for planning and implementing scalable data exchange capabilities, e.g., the enterprise architecture activity that is responsible for the standardization of technology across the entire agency and the data standards activity that defines how the FDA and its stakeholders will exchange data, are grossly understaffed for an agency the size of the FDA.

While the IT-staff-to-total-staff ratio approaches industry benchmarks at 5.8/100, it is important to recognize that these benchmarks do not take into account either the complexity of the FDA scientific mission or the need for the FDA to support the development of national/international information sharing capability.

Recommendation 6: Information Technology Workforce Improvement

- Define required skill sets for the FDA's information technology workforce
- Develop an informatics fellowship program
- Develop strategies for recruitment and retention of critical informatics staff especially in the areas of 'new science'
- Develop and implement strategies for professional development that will facilitate the Agency's need to operate at the forefront of regulatory science

Finding 7: Legislative Support for information technology is not being leveraged effectively to progress the quality, safety, and efficacy missions of the FDA.

There is very strong consensus that the nation could substantially benefit from effective data sharing networks to support quality, safety and efficacy activities. These complex data sharing infrastructures are dependent on the adoption of technical and scientific standards. The FDA staff was emphatic that legislative mandates that supported standards-based electronic submission of applications and clinical data would dramatically speed time to development of these critical capabilities – the Subcommittee concurs.

Recommendation 7: Legislative Support for information technology is not being leveraged effectively to progress the quality, safety, and efficacy mission of the FDA.

- Develop policy and legislative expertise for the IT domain. This should include basic issues such as technical standards but should also include the ability to promote legislative activities around emerging technologies
- Ensure that FDA guidelines are in synch with judicial and legislative activities. In the case of recommendations by the FDA Task Force on Counterfeit Drugs, the FDA guidelines, judicial actions, and legislation are not synched up which confuses industry and stakeholders, prevents investment, and ultimately damages attempts to build information infrastructure to counter a serious public health and commerce-related problem.

7. Glossary of IT Terminology

Business Continuity Planning: “Business Continuity Planning (BCP) is a *methodology* used to create and validate a practiced *logistical plan* for how an *organization* will recover and restore partially or completely interrupted *critical* function(s) within a predetermined time after a *disaster* or extended disruption. The logistical plan is called a Business Continuity Plan.” **(source: wikipedia).**

Context for the FDA: the FDA does not have a business continuity plan (BCP) or even its subset constituent, Disaster Recovery Plan (DRP), in the sense of a timely recovery of operations from a major disruption of normal business activity. The current practice of tape backups of information stores constitutes but one relatively minor component of a true logistical plan. An enterprise disaster recovery plan with tiered priorities by process functional importance (meaning recovery times ranging from seconds to hours to days) must be in place especially as the Agency embarks on scientific frontiers of even greater data complexity. The move to a new data facility at White Oaks presents a window of opportunity. From the report discussion on **enterprise architecture**, it follows that the major cost component of an FDA BCP/DRP project is not the hardware or facilities (although these are substantial) but the personnel budget for **business integrators**, for timely input of process knowledge by the line function over the project timeline.

Business Integrator: Business integrators provide the “what and why”, as opposed to the “how” of information technology, to insure alignment between IT investments and organizational strategy. They thus play a role in implementation of priorities in large enterprises at a level of granularity finer than that set by high level councils or executive teams. For effective implementation of this role, the ideal business integrator is an experienced “star” from the line function with a degree of know-how about IT.

Context for the FDA: Large scale IT transformation projects can succeed only if the project management office is staffed with domain experts (FDA regulatory scientists) who are familiar with Agency processes and use cases. New positions should be created and placed in a central role in the IT Transformation and/or **Enterprise Architecture** group and answerable to the office of the CIO and CSO. Some of the more IT savvy FDA scientists, preferably with many years of experience at the Agency should be detailed full time to these new roles over the life of the project. The number of positions would be set to insure connections to and coverage of domain knowledge of all centers and offices; budgetary impact comes from the cost of back-filling vacated line roles.

Enterprise Architecture: “Enterprise Architecture is the practice of applying a comprehensive and rigorous method for describing a

current and/or future structure and behavior for an organization's processes, information systems, personnel and organizational sub-units, so that they align with the organization's core goals and strategic direction. Although often associated strictly with information technology, it relates more broadly to the practice of business optimization in that it addresses business architecture, performance management, organizational structure and process architecture as well." (**source: wikipedia**).

Context for the FDA: The enterprise architecture group at the FDA is a technologically talented but small and under funded department; it is viewed solely as an information technology function. In particular the group suffers from the absence of **business integrators** in the group or elsewhere at the FDA.

Instrument Bridge: an extension of the **network bridge** concept from the IEEE networking technology glossary; the terminology, instrument bridge, highlights the logical separation of scientific instruments from administrative computers (e.g., email servers) on the computer network of a science-intensive organization.

Context for the FDA: The FDA shares a challenge common to all data-intensive scientific organizations: a fundamental incompatibility between current best practices in network management for administrative functions (e.g., email) and network management for scientific instruments. The former is driven by cyber security issues including defense against intrusions, email viruses and internet worms. The latter requires extended uptime for experiments with long runs and connection to Internet2 (the new information superhighway restricted only to research organizations) – just a few illustrations of the difference in management philosophy. Modern data intensive science cannot be done on an administrative network optimized for cyber defense; new network technologies that allow both networks to coexist is the answer. Since the network impacts everyone at the Agency, this is another example of a project that is enterprise architectural in scope.

Server Virtualization: "or virtual private server is a method of partitioning a physical server computer into multiple servers that each has the appearance and capabilities of running on its own dedicated machine. Each virtual server can run its own full-fledged operating system, and each server can be independently rebooted. The practice of partitioning a single server so that it appears as multiple servers has long been common practice in *mainframe computers*, but has seen a resurgence lately with the development of virtualization software and technologies for other architectures." (**source: wikipedia**).

Context for the FDA: The FDA has a highly diverse array of servers (computers) and this diversity serves no strategic purpose – it just happened over time. Indeed, the ensuing complexity consumes greater

resources, including staff and/or consultants to support outdated operating systems from the 1980s and an extended procurement cycle for replacement machines. But because of the close coupling of applications to server technology, this situation cannot be remediated by simply pulling the plug on older servers and technology outliers and a forced migration of their hosted applications to a smaller set of standard server configurations. It will be a project of significant scale to triage the large universe of applications – the major cost will be compensation of **business integrators** (regulatory scientists) as they input their FDA process knowledge. But the benefits will outweigh the costs. Organizations that have migrated to this technology can “procure” a new server for a vital application in minutes. The FDA server procurement process can take six months, including scenes of an overwhelmed staff unable to uncrate newly arrived equipment.

Storage Area Network (SAN): the technology architecture for attaching remote storage devices over a network so that to the computer operating system on a server, the storage devices appear as locally attached. Their relatively high cost is justified in large enterprises because of their utility in business continuity planning.

Context for the FDA: As with any other data intensive organization, the cumulative data storage at the FDA is measured in terabytes (trillions of bytes) and is transitioning to the petabyte (1,000 terabytes) scale. The current best practice in storage technology is the SAN – or storage area network. SANs are the cornerstone in enabling enterprise-wide data pooling and flow through an information supply chain. The FDA has SANs, in fact over a dozen. They are not connected with each other as a single pool but have been characterized as “information puddles” with incompatible standards and thus unusable in their rightful place as a cornerstone of business continuity planning. For the FDA, an enterprise wide SAN project is not a question of buying the right stuff, but the difficult process of engaging business integrators in the line function to establish the storage strategy.