FDA Science and Mission at Risk

Report of the Subcommittee on Science and Technology

PREPARED FOR
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FDA Mission Statement

"The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health."

Section 1

Executive Summary

1.1 Overview

A strong Food and Drug Administration (FDA) is crucial for the health of our country. The benefits of a robust, progressive Agency are enormous; the risks of a debilitated, under-performing organization are incalculable.

The FDA constitutes a critical component of our nation's healthcare delivery and public health system. The FDA, as much as any public or private sector institution in this country, touches the lives, health and wellbeing of all Americans and is integral to the nation's economy and its security.

The FDA's responsibilities for protecting the health of Americans are far-reaching. The FDA protects our nation's food supply through regulatory activities designed to cover 80 percent of the food consumed in this country. The FDA also regulates all drugs, human vaccines, and medical devices, and hence plays a critical role in ensuring the appropriate safety and efficacy of rapidly emerging medical products. Indeed, countries around the world have historically looked to the FDA for guidance on sound, science-based regulation, and have looked to its product approval decisions as accurate determinations of new product safety.

The FDA is also central to the economic health of the nation, regulating approximately $1 trillion in consumer products or 25 cents of every consumer dollar expended in this country annually. The industries that FDA regulates are among the most successful and innovative in our society, and are among the few that contribute to a positive balance of trade with other countries.

The importance of the FDA in the nation's security is similarly profound. The FDA plays a central role in protecting the nation from the potential effects of terrorist attacks[1], such as anthrax, smallpox, attacks on the food supply, nerve agent attacks and radioactive contamination, as well as from naturally occurring threats, such as SARS, West Nile virus and avian influenza.

[1] http://www.fda.gov/fdac/features/2004/104_terror.html

Thus, the nation is at risk if FDA science is at risk. In recognition of this threat, in December 2006, FDA Commissioner Andrew von Eschenbach, MD requested that the Science Board, which is the Advisory Board to the Commissioner, form a Subcommittee to assess whether science[2] and technology at the FDA can support current and future regulatory needs. Specifically, the Subcommittee's charge was to identify 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 during the next decade. The Science and Technology Subcommittee of the FDA Science Board (hereafter called the Subcommittee) was composed of three members of the Science Board and other experts representing industry, academia and other government agencies, and included individuals with extensive knowledge of cutting-edge research. Most importantly, these experts possess a deep understanding of regulatory science and the core mission of the Agency[3]. This report is the product of that assessment.

The Subcommittee concluded that science at the FDA is in a precarious position: the Agency suffers from serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities.

The Subcommittee found that the deficiency has two sources:

- The demands on the FDA have soared due to 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.
- The resources have not increased in proportion to the demands. The result is that the scientific demands on the Agency far exceed its capacity to respond. This imbalance is imposing a significant risk to the integrity of the food, drug, cosmetic and device regulatory system, and hence the safety of the public.

The Subcommittee further noted that the impact of the deficiency is profound precisely because science is at the heart of everything FDA does. The Agency will flounder and ultimately fail without a strong scientific foundation. That foundation rests on three pillars. The first pillar is strong selective scientific research programs that are appropriately mission-supportive, in all areas of FDA responsibility. This research is critical because it is not conducted by other public or private entities, but is fundamental to the discharge of FDA's statutory responsibilities to protect and promote the public health. The second pillar is excellent staff with cutting-edge scientific expertise appropriate to the mission. This expertise includes the ability to access, understand

[2] For the purpose of this report, the Subcommittee elected to use the term "science" broadly to encompass all of the disciplines and activities within the FDA that have a scientific basis, e.g., research, review of submitted applications and petitions, development of scientific policy, guidelines and procedures, and the analytical and inspection responsibilities of the office of regulatory affairs.
[3] See Appendix A, *Subcommittee to the FDA Science Board*.

and evaluate science; effectively apply this science to the regulatory process; and communicate the implications of its findings for product safety and efficacy to the public. The third pillar is an information infrastructure and processing capability that ensures the FDA has access to the best data and information necessary to support the regulatory science required to fulfill FDA's mission

1.2 Major Findings

The Subcommittee found substantial weaknesses across the Agency, with the possible exception of some drug and medical device review functions funded by industry user fees. There are several areas of greatest concern, however, which form the basis for this report's most significant findings.

1.2.1 The FDA cannot fulfill its mission because its scientific base has eroded and its scientific organizational structure is weak.

The nation's food supply is at risk. Crisis management in FDA's two food safety centers, Center for Food Safety and Applied Nutrition (CFSAN) and Center for Veterinary Medicine (CVM), has drawn attention and resources away from FDA's ability to develop the science base and infrastructure needed to efficiently support innovation in the food industry, provide effective routine surveillance, and conduct emergency outbreak investigation activities to protect the food supply.

FDA's inability to keep up with scientific advances means that American lives are at risk. While the world of drug discovery and development has undergone revolutionary change — shifting from cellular to molecular and gene-based approaches — FDA's evaluation methods have remained largely unchanged over the last half century. Likewise, evaluation methods have not kept pace with major advances in medical devices and use of products in combination.

The world looks to FDA as a leader — to integrate emerging understandings of biology with medicine, technology and computational mathematics in ways that will lead to successful disease therapies. Today, not only can the Agency not lead, it cannot even keep up with the advances in science.

Due to constrained resources and lack of adequate staff, FDA is engaged in reactive regulatory priority setting or a fire-fighting regulatory posture instead of pursuing a culture of proactive regulatory science. This is particularly true for CFSAN and CVM, which are in a state of crisis (Finding 3.1.1). The FDA cannot adequately monitor development of food and medical products because it is unable to keep up with scientific advances (Finding 3.1.2). The Subcommittee identified the following eight emerging science and technologies that are most challenging the FDA: systems biology (including genomics and other "omics"), wireless healthcare devices, nanotechnology, medical imaging, robotics, cell- and tissue-based products, regenerative medicine, and combination products. Each of these emerging areas is developing at an exponential rate and each generates novel scientific, analytic, laboratory and/or information requirements. The FDA cannot fulfill its surveillance mission because of inadequate staff and IT resources to implement cutting-edge approaches to modeling, risk assessment and data analysis (Finding 3.1.3). The FDA lacks a coherent scientific structure and vision as a result of weak organizational infrastructure (Finding 3.1.4). Strong scientific leadership is needed at all levels to develop a new vision to build a strong science base within the Agency, and in parallel, this leadership must establish optimal mechanisms to access the best scientific knowledge and expertise from throughout the government, academia and industry. Consistent and rigorous peer reviews of programs and processes, which are currently lacking, are critical for wise utilization of resources and for rebuilding the Agency's ability to implement its science-based regulatory responsibilities effectively.

1.2.2 The FDA cannot fulfill its mission because its scientific workforce does not have sufficient capacity and capability.

The Subcommittee found that despite the significant increase in workload during the past two decades, in 2007 the number of appropriated personnel remained essentially the same — resulting in major gaps of scientific expertise in key areas[4]. More importantly, despite the critical need for a highly trained workforce to fulfill its mission, the FDA faces substantial recruitment and retention challenges. The turnover rate in FDA science staff in key scientific areas is twice that of other government agencies, *GAO-02-958 PDUFA User Fees* (Finding 3.2.1). There are insufficient programs of measurement to determine worker performance (Finding 3.2.2). There is insufficient investment in professional development, which means that the workforce does not keep up with scientific advances (Finding 3.2.3). Finally, for various reasons, the FDA does not have sufficiently extensive collaboration with external scientists, thus limiting infusion of new knowledge and missing opportunities to leverage resources (Finding 3.2.4).

[4] See Appendix B, *The State of Science at the Food and Drug Administration*.

FDA's failure to retain and motivate its workforce puts FDA's mission at risk. Inadequately trained scientists are generally risk-averse, and tend to give no decision, a slow decision or, even worse, the wrong decision on regulatory approval or disapproval. During our encounters with staff and center leadership, we were struck by the near unanimity that the shortage of science staff (due to lack of resources to hire) and the inability to recruit and retain needed expertise are serious, longstanding challenges. Internal expertise and experience to provide the science capability and capacity needed in highly specialized and fast-evolving areas is disturbingly limited. The lack of a trained workforce means that the FDA is ineffective in responding to emerging fields that require individuals and work teams with multidisciplinary skills built on very complex, highly specialized, often esoteric bodies of knowledge.

1.2.3 The FDA cannot fulfill its mission because its information technology (IT) infrastructure is inadequate.

The Subcommittee was extremely disturbed at the state of the FDA IT infrastructure. While some good progress is being made to improve information sciences and technology (Finding 3.3.1), the Subcommittee found that the FDA lacks the IT infrastructure necessary to meet its mandate (Finding 3.3.2). It also found that the FDA has insufficient access to data and cannot effectively regulate products based on new science due to lack of a supportive IT infrastructure (Finding 3.3.3). The Subcommittee noted that the FDA IT infrastructure is obsolete, unstable and lacks controls to execute effective disaster recovery protocols that ensure continuity of operations when systems are compromised (Finding 3.3.4). Finally, the IT workforce is insufficient (Finding 3.3.5).

The IT situation at FDA is problematic at best — and at worst it is dangerous. Many of the FDA systems reside on technology that has been in service beyond the usual life cycle. Systems fail frequently, and even email systems are unstable — most recently during an *E.coli* food contamination investigation. More importantly, reports of product dangers are not rapidly compared and analyzed, inspectors' reports are still hand written and slow to work their way through the compliance system, and the system for managing imported products cannot communicate with Customs and other government systems (and often miss significant product arrivals because the system cannot even distinguish, for example, between road salt and table salt).

There are inadequate emergency backup systems in place: recent system failures have resulted in loss of FDA data. Critical data reside in large warehouses sequestered in piles and piles of paper documents. There is no backup of these records, which include valuable clinical

trial data. The FDA has inadequate extramural funding programs and collaborations to accelerate the development of critical health information exchanges in order to support clinical trials and pharmacovigilance activities.

1.3 Summary Statement and Recommendations

Although this Subcommittee was asked to review gaps in scientific expertise and technology and not to assess available resources, it rapidly became apparent that the gaps were so intertwined with two decades of inadequate funding that it was impossible to assess technology without also assessing resources. This conclusion is based on an analysis of the reports of previous review committees[5][6][7][8][9], each of which was given similar charges during the past 50 years. The themes raised by the previous committees, as well as the present Subcommittee, are very consistent: 1) the criticality of high-quality science to the regulatory mission; 2) the need for the science to be mission driven; 3) persistent expressions of dissatisfaction with the quality and credibility of the scientific programs; 4) consistent calls for major change in the organization and management of the Agency's scientific endeavors; and 5) consistent inability of the Agency to implement needed changes. Not all of the reasons for failure are apparent, but our analysis, as well as those of previous committees, revealed a very dangerous trend: the continual expansion of FDA responsibilities coupled with a dramatic decline in resources, particularly during the past two decades.

In contrast to previous reviews that warned crises would arise if funding issues were not addressed, recent events and our findings indicate that some of those crises are now realities and American lives are at risk.

[5] Edwards Commission Report: Final Report of the Advisory Committee on the Food and Drug Administration, Advisory Committee on the Food and Drug Administration, U.S. Department of Health and Human Services, 1991
[6] CBER Report: Review of Research Programs, Center for Biologics Evaluation and Research, Food and Drug Administration, Subcommittee for Review of CBER Research, Science Board to the food and Drug Administration, *Final Report*, October 1998
[7] CFSAN Report*:* Review of Research Programs, Center for Food Safety and Applied Nutrition, food and Drug Administration, April 1999
[8] CDRH Report: Science at Work at CDRH: A Report on the Role of Science in the Regulatory Process, Submitted by the External Review Committee, Center for Devices and Radiological Health, Final Report, November 2001
[9] See for example, David Korn. FDA Under Siege: The Public at Risk, Science 276:1627, 1997 and http://www.cfsan.fda.gov/~frf/sxsbra.html.

Our Subcommittee, therefore, spent considerable effort garnering as much information as possible about the current roles and responsibilities of Agency staff, available resources, the current status of science within the Agency, and the implication of emerging science for the future of FDA and the public's health. We found that FDA's resource shortfalls have resulted in a plethora of inadequacies that threaten our society — including, but not limited to, inadequate inspections of manufacturers, a dearth of scientists who understand emerging new technologies, inability to speed the development of new therapies, an import system that is badly broken, a food supply that grows riskier each year, and an information infrastructure that was identified as a source of risk in every Center and program reviewed by the Subcommittee. We conclude that FDA can no longer fulfill its mission without substantial and sustained additional appropriations. Numerous reports by the National Academies of Science (including two recent reports by the Institute of Medicine [IOM] on drug safety)[10], the Government Accountability Office (GAO), the Health and Human Services (HHS) Inspector General, Congressional committees, and other expert groups have come to the same conclusion. The opinion of these studies is unanimous — current gaps are due to chronic underfunding of the Agency, and if these gaps are not addressed immediately, FDA is in jeopardy of losing its remaining dedicated staff. The extraordinary efforts of these committed FDA staff members are the very reason further catastrophic food and drug events have been averted.

Although there is indeed great urgency to stem the tide of continued deterioration in the science that supports the regulatory decisions of the FDA, the magnitude of changes that are needed will require a phased approach based on a well-thought-out plan. Strategic plans must be developed within a strengthened science organization, as recommended in this report. Recruitment of outstanding talent with up-to-date skills will also take time. However, there must be an immediate commitment to make the needed investments in order to recruit the most outstanding talent. For example, during the time of our review, the directorship of two of the largest FDA centers, CFSAN and the Center for Drug Evaluation and Research (CDER), became vacant. It will be difficult, if not impossible, to recruit the best leaders unless there is assurance that adequate resources and staff will be available to address the challenges.

The magnitude of the resources required to restore scientific capability and capacity is substantial. The IOM has indicated the minimum immediate appropriation necessary to address urgent needs in drug safety is $350 million. And the Grocery Manufacturers/Food Products Association has recommended a minimum of $450 million over five

[10] See IOM (Institute of Medicine) 2007. Challenges for the FDA: The Future of Drug Safety. Washington, DC: The National Academies Press
IOM (Institute of Medicine) 2007. The Future of Drug Safety: Promoting and Protecting the Health of the Public. Washington, DC: The National Academies Press.

years is needed to ensure food safety[11]. Other groups, for example the Coalition for a Stronger FDA (co-chaired by the last three HHS Secretaries and endorsed by a number of former FDA Commissioners), have stated that a 15 percent increase in appropriations per year during the next five years will be required[12]. The Subcommittee believes that these increases would still be an insufficient amount to allow the Agency to initiate and support all of the changes necessary to fulfill its mission. Thus, we strongly recommend that the most immediate increases be used to address those critical gaps identified in this report.

We recognize that adequate resources — human and financial — alone will not be sufficient to repair the deteriorating state of science at FDA, which is why we also recommend significant restructuring. But without a substantial increase in resources, the Agency is powerless to improve its performance, will fall further behind, and will be unable to meet either the mandates of Congress or the expectations of the American public. This will damage not only the health of the population of the US, but also the health of our economy. Currently each American pays about a penny and a half a day for the FDA; an increase to three cents daily would not, in our view, be a great price to pay for the assurance that our food and drug supply is, indeed, the best and safest in the world.

1.4 The Structure of This Report

The Subcommittee's report is structured as follows. It first provides the context within which the FDA operates. The subsequent section discusses key findings and recommendations, organized into three categories based on the three pillars deemed critical to the FDA's ability to fulfill its mission: Science, Workforce and Information Infrastructure. The final section provides a concluding statement about the study.

The Appendices include not only source material for the Subcommittee's findings and recommendations, but also, in Appendices C–K, detail on the gaps in science and technology for each of the FDA Centers and the cross-cutting issues reviewed by this Subcommittee (genomics, surveillance/biostatistics and information technology).

[11] http://www.fpa-food.org/content/newsroom/article.asp?id=463, Coalition for Stronger FDA (news release, September 25, 2006

[12] http://www.fdacoalition.org/news.php, FDA Coalition Seeks Increases to Agency Budget (press release, February 6, 2007)

Section 2 Context: The Changing FDA Environment

2.1 Growing Disparity between Responsibilities and Resources

When the Federal Food, Drug, and Cosmetic Act was originally enacted in 1938, the regulatory and compliance issues FDA faced were comparatively simple. From that modest beginning, however, FDA's role as gatekeeper to new products has expanded enormously[13]. 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, as well as to review and approve the safety and effectiveness of new human drugs, new animal drugs, human biological products and medical devices for human use. As a practical matter, today no new pharmaceutical product or medical technology can be used in the US 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 newly marketed dietary supplements.

FDA's responsibilities have continued to expand. During the past two decades Congress has enacted 125 statutes that directly impact FDA's regulatory responsibilities — an average of more than six each year — in addition to the core provisions of the 1938 Act itself and its amendments from 1939 to1987[14]. 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 entirely new regulatory programs. Virtually all statutes require some type of scientific knowledge or expertise for the Agency to adequately address them, and in some cases may require laboratory research. Yet none of these statutes has been accompanied by an appropriation of the new personnel and increased funding necessary to enable adequate implementation. In fact, during the same 20-year period from 1988 to 2007, while faced with 123 new statutes, FDA gained through appropriation only 646 employees — an increase of 9 percent — and lost more than $300 million to inflation[15]. The appropriated budget of FDA for 2007 was approximately $1.6 billion. The number of appropriated personnel in 2007 was roughly the same number as was appropriated 15 years earlier. This reality, combined with a burgeoning industry as

[13] See Appendix B, *The State of Science at the Food and Drug Administration*.
[14] 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 new human and animal drugs.
[15] See Appendix B, *The State of Science at the Food and Drug Administration*.

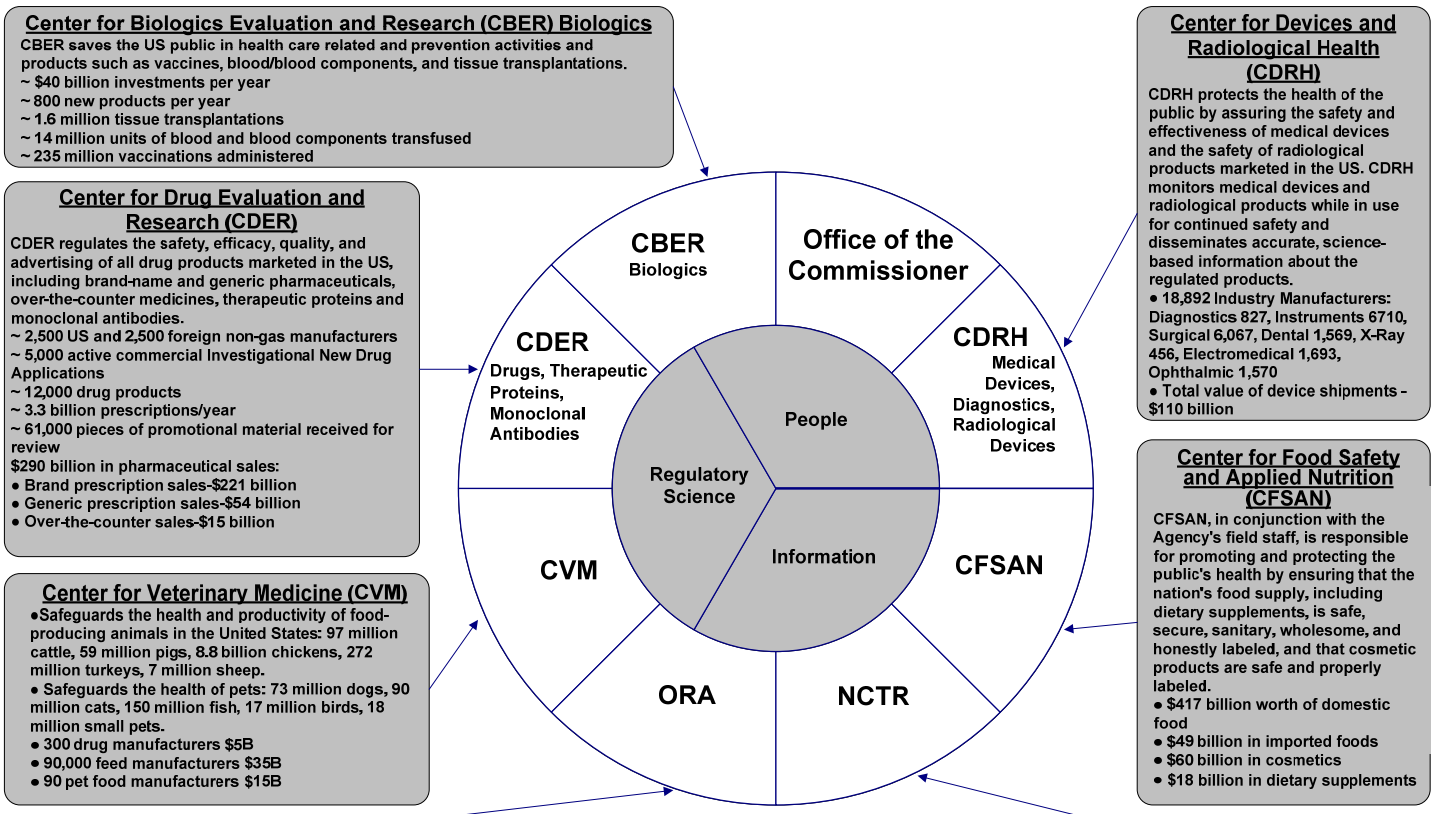
documented below, has made it increasingly impossible for FDA to maintain its historic public health mission. Since 1992 user fees have played a critical role in support of pre-market review and approval functions of new medical products[16]. Because these funds are in addition to appropriated funds and are adjusted for inflation each year, the serious decline in appropriated support for other activities — many of which are core regulatory activities, but not covered by user fees — has not been generally appreciated by those who look only at bottom-line budget figures.

Figures 1 and 2 illustrate the magnitude of FDA's regulatory responsibilities in 2006 (costs are approximate and include pre- and post-market activities and product quality). For example, the Center for Devices and Radiological Health (CDRH) regulated manufacturers with industry sales of $110 billion. The CFSAN was responsible for regulating $417 billion worth of domestic food, $49 billion in imported foods, $60 billion in cosmetics and $18 billion in dietary supplements. The CDER regulated $275 billion in pharmaceutical sales, 2,500 US manufacturers and 2,500 foreign manufacturers. The CVM oversaw the safety of more than 10 billion food-producing animals and 200 million pets, and regulates more than 90,000 manufacturers. The Center for Biologics Evaluation and Research (CBER) reviews more than 800 new products and $40 billion in investments every year. The Office of Regulatory Affairs (ORA) regulates more than 123,000 establishments. Overall in 2006, FDA regulated more than 375,000 establishments worldwide, covering every continent and almost 100 countries.

[16] See Appendix B, *The State of Science at the Food and Drug Administration*.

Figure 1: Food and Drug Administration – Regulatory Industry (FY2006)

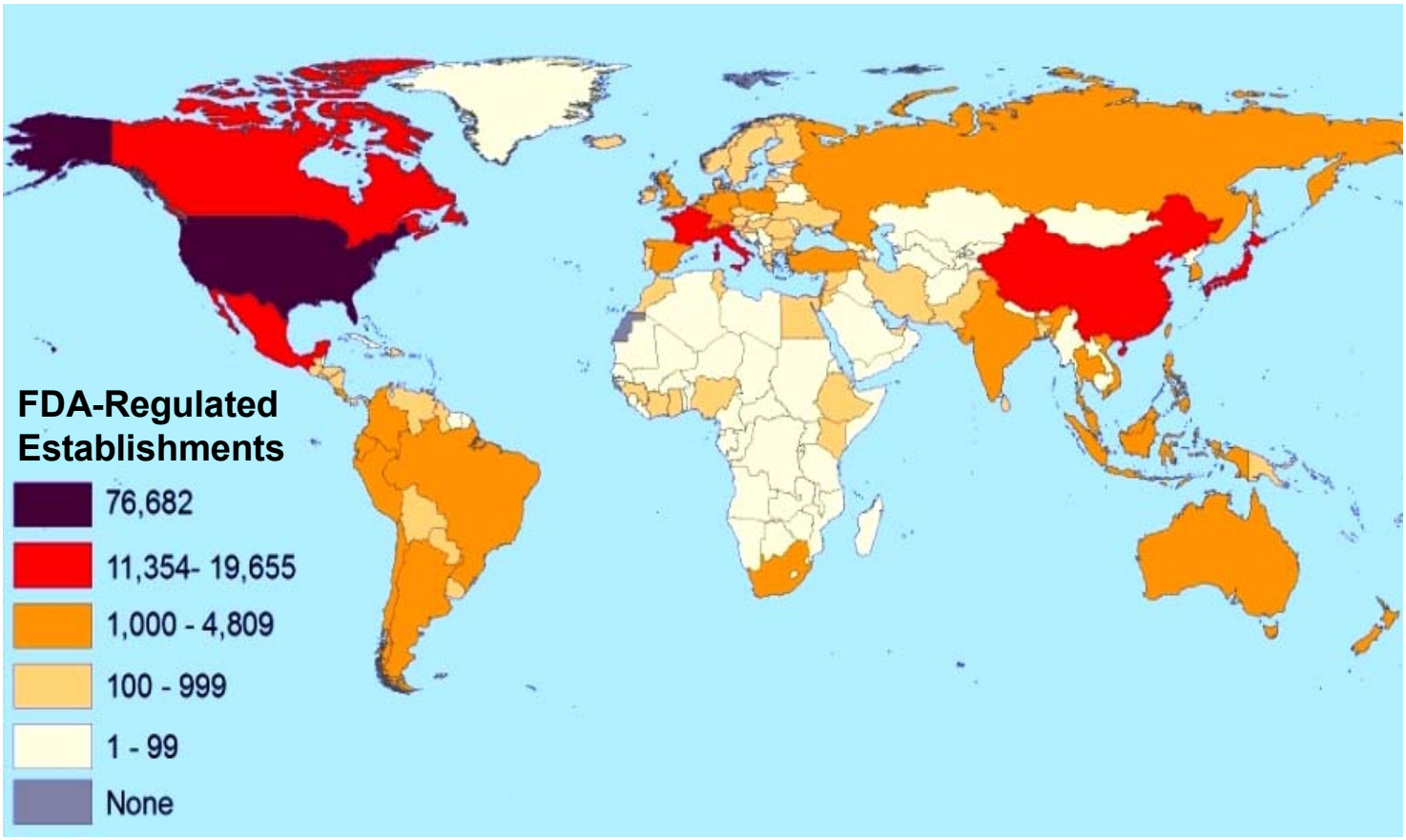
The People, Science and Information Needed to Support Innovation, Grow Industries, and Protect the Public Both in Our Country and Around the World



Legend:		
AERS – Adverse Even Reporting System	CVM – Center for Veterinary Medicine	NCTR – National Center for Toxicological Research
BLA – Biologic License Application	FY – Fiscal Year	ORA – Office of Regulatory Affairs
CBER – Center for Biologics Evaluation and Research	GMP – Good Manufacturing Practice	OTC – Over the Counter
CDER – Center for Drug Evaluation and Research	GRAS – Generally Recognized as Safe	PMA – Pre-Market Approval Application
CDRH – Center for Devices and Radiological Health	IDE – Investigational Device Exemption	VAERS – Vaccines Adverse Even Reporting System
CFSAN – Center for Food Safety and Applied Nutrition	IND – Investigational New Drug	510(k) – Pre-Market Notification Application

Source: FDA 10/02/07

Figure 2: The Breadth of FDA Responsibilities by Number of Establishments



Source: FDA 10/02/07

2.2 The Criticality of Science

Prior to 1970, the FDA was primarily a law enforcement Agency and relied far less on science: the issues of adulteration and misbranding could be handled by well-trained inspectors. The need for PhDs and MDs was modest, and very few were employed by the Agency. Beginning in the 1970s however, FDA became a modern science-based regulatory Agency[17]. The bulk of its work shifted from the courts to regulatory decisions made within the Agency with the advent of pre-market review and approval requirements for FDA-regulated products. Science forms the basis of all regulatory decisions. Those that do not have adequate scientific support are thus subject to delays, or worse, poor decisions. Therefore, effective regulation requires that the scientific competency within FDA matches or exceeds an applicant's knowledge.

[17] See Appendix B, *The State of Science at the Food and Drug Administration*.

Today, science at FDA encompasses the totality of technical knowledge regarding foods and medical treatments, including pre-market review, efficacy/safety assessment, surveillance of marketed product adverse events, and marketed product quality and safety. Figure 3 highlights the critical role of science-based decisions to fulfilling FDA's mission. The bulk of the Agency's activities involve reviewing new drugs, biologics, medical devices and additives. It is clear from this list that the FDA must master science at the molecular and nanoscale, and be able to detect, assess and respond to the growing risks resulting from globalization.

Appendix L gives a detailed summary of how FDA regulatory activities are supported by its scientific capacities. FDA needs to have access to expertise from a diverse set of necessary scientific disciplines, ranging from molecular biology to nuclear physics and engineering. The activities for which FDA needs such expertise is wide-ranging: the review and assessment of *in vitro* bench data; animal and human clinical data; methods development; facilities inspection; and development of technical and scientific standards (domestic and international harmonization of such standards) for preclinical assessment, product development, manufacturing, packaging standards, food safety standards and food processing technologies. An even broader range of activities related to surveillance of adverse events is needed with marketed products: surveillance and efficacy and safety assessments need support. These iterative and complex activities consist of multiple sublevels of activity, such as science-based interactions with third parties. Surveillance also requires an array of analytic activities as well as extensive risk communications activities.

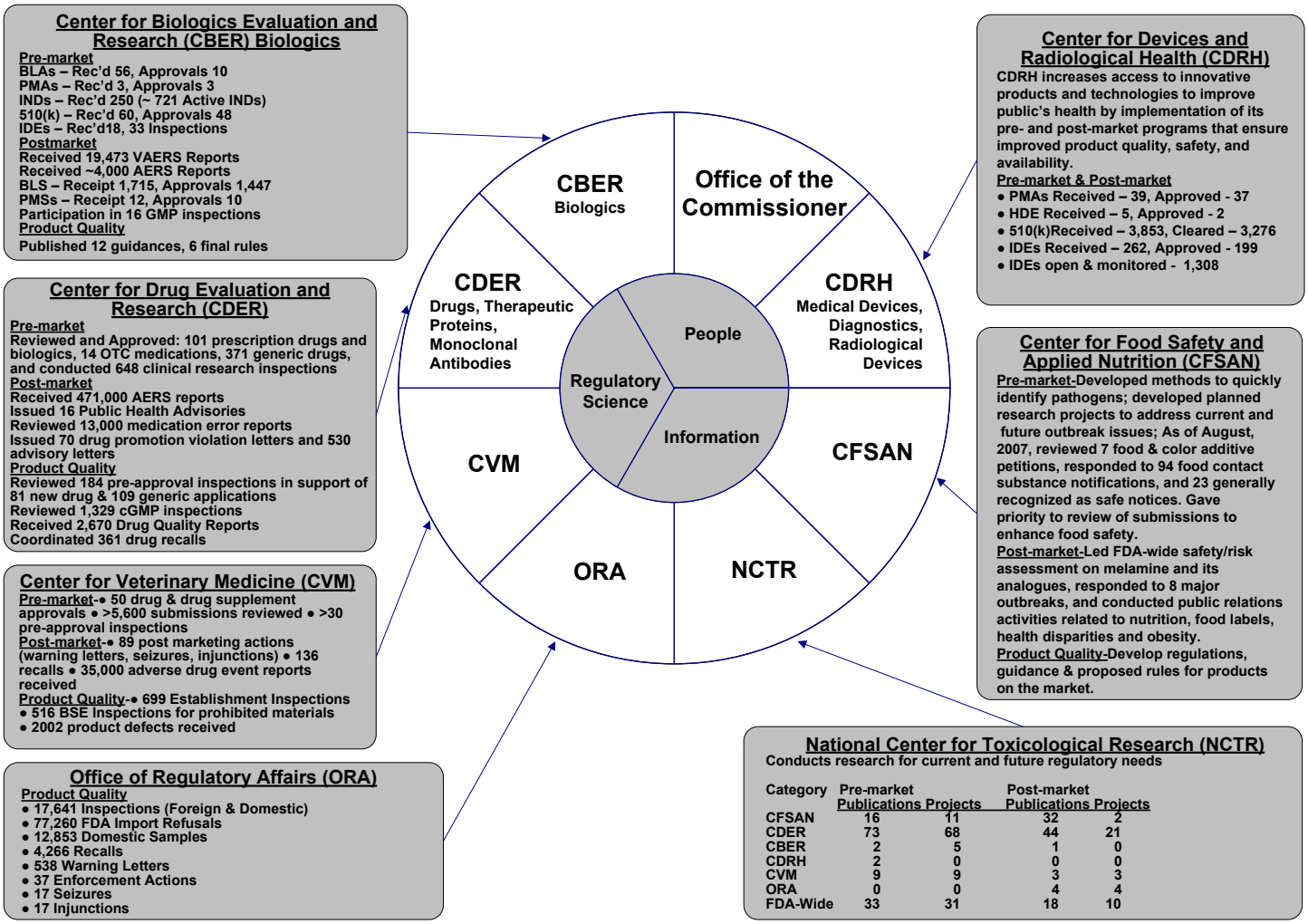
FDA must have the scientific staff and resources to undertake the regulatory research that will provide a basis to: 1) improve capacity for safety and efficacy evaluations and monitoring of candidate and licensed products, 2) modernize current regulatory pathways, and 3) develop new regulatory pathways where there are currently none. Much of this research must be undertaken by FDA because it is mission critical, and because it either cannot or will not be done by other government agencies or industry. Indeed, such recent, high-impact FDA research as the development of better preclinical tests of oxidative chemistry and NMR and mass spectroscopy to predict safety and efficacy performance in clinical trials of hemoglobin-based oxygen carrier products could not have taken place in another Agency.

Other examples of vital activities that are FDA specific include the development and testing of West Nile Virus standards and the performance of *in vitro* tests that supported policy making and the crafting of guidance to safeguard the nation's blood supply before others even suspected the virus was transmissible by blood. Similarly, the FDA led other efforts for blood donor testing for Chagas disease and transmissible spongiform encephalopathies. FDA scientists developed new models for assessment of computer-assisted diagnostic

systems, including those for lung and breast cancer screening, as well as test methods for pulse oximeters and high-intensity ultrasound. FDA laboratory efforts were the basis for the development of performance requirements for measurement instruments, as well as appropriate measurement procedures in a preclinical testing guidance for extracorporeal shock lithotripsy for disruption of urethral calculi. This guidance eventually led to two international consensus standards. FDA scientists provided expertise in gene expression profiling, proteomics, metabolomics and toxicogenomics for detailed and comprehensive evaluation of the voluntary genomics data submissions "Guidance for Industry: Pharmacogenomic Data Submissions."

In summary, getting the science right is critical to FDA's ability to fulfill its mission. Decisions made in regulation development, pre-market approvals, legal actions and related public health emergencies must be based on understanding of contemporary and emerging science within the context of the risk analysis paradigm. Indeed it will also increasingly be true of assessing efficacy, particularly as we move into the era of the personalization of medicine.

Figure 3: Food and Drug Administration – Regulatory Activity (FY2006)



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CFSAN – Center for Food Safety and Applied Nutrition	IND – Investigational New Drug	510(k) – Pre-Market Notification Application

Source: FDA 10/02/07

2.3 The Changing Nature of Science

The central challenge for the FDA is to protect consumers by making use of the best possible science while supporting the efficient development of new products. The scientific paradigm of the past 30 years, which was based on the targeting of specific enzymes, receptors and ion channels, and advances in understanding nutrition, has enabled the discovery and development of important medicines and vaccines that have had enormous impacts on human and animal health. Yet effective treatments for a wide variety of diseases, such as many forms of cancer, Alzheimer's Disease and Parkinson's Disease have been difficult to find because of the complexity of the molecular bases of these diseases.

The level of scientific understanding has changed in the following two important ways:

- A complete parts list of all human genes is becoming increasingly available so that the component parts of the complex system can be delineated.
- A view of biology as an information science has emerged.

It is clear that biological information is acquired, transmitted, integrated and distributed by biological networks[18] to molecular machines[19]. These two insights have generated a whole new strategy: a *systems approach* to understanding health and disease. This systems view has significant implications for products or tools used in diagnosis, therapy and even prevention. It provides completely new and powerful strategies for approaching these tools of contemporary medicine because we are now moving from having the complete parts list to learning how these parts function together in networks and systems[20]. The challenge that faces the FDA is that a systems approach requires a cross-disciplinary environment where biology, medicine technology and computation/mathematics can be seamlessly integrated. Coupled with this more integrative approach to biological information and its likely impact on drug discovery and the prediction of drug efficacy and safety, the integration of individual genomic information with technological advances in quantitative, unbiased and hypothesis-driven biomarkers of drug action is likely to hasten the progressive personalization of medicine.

[18] E.g., the universe of genes and the information they contain.
[19] E.g., the protein products that execute the functions of life.
[20] The systems view attempts to describe disease-perturbed dynamic biological networks so that we can understand the roles they play in the progression of individual diseases. To delineate these networks, data of many different types must be generated, integrated and finally modeled dynamically to explain biological complexity. This data will include all of the measurements coming from the 'omics,' including DNA, RNA, protein metabolites, phenotyes, etc.

Aside from these shifts in the substrate of regulatory science, the Agency is likely also to be challenged with an increasing mix of therapeutic modalities and the methods by which they are delivered. Thus, the current focus on biologicals is likely to be complemented increasingly by advances in gene- and stem-cell-based therapeutics, while attempts at targeted delivery of all therapeutic modalities is only likely to increase. Finally, advances in information processing, clinical trial design and access to population-wide phenotypic and genotypic databases will present the Agency with opportunities that will critically depend on the workforce and collaborations necessary to exploit them.

Other forces are revolutionizing both medicine and biology. These include the development of powerful new measurement (nanotechnology) and *in vivo* imaging technologies, as well as the pioneering of new mathematical and computational tools for acquiring storing, validating, mining, integrating, visualizing and modeling biological information. How information is transmitted is changing rapidly (wireless). Chemistry and engineering advances have led to products with new size attributes (nano-particles and machines) that lead to the potential way they will interact with humans in novel ways. The application of robotics is revolutionizing medical device design, product and pharmaceutical manufacturing. Reported advances in cell- and tissue-based products are leading to the potential for true regenerative medicine. Advances in medical imaging offer the potential to understand drug, receptor, disease and patient relationships in promising ways. With the increasing ability to combine product components and subunits in novel ways the division of FDA-regulated products (into drugs, devices, biologics, etc.) is becoming less relevant.

The promise of the resulting paradigm shift is that medicine will move progressively from the assessment of drug efficacy and safety based on large average effects detected in clinical trials to a more personal paradigm. Realization of this possibility is based on overcoming significant medical, scientific, technological, information, social and political hurdles. Thus, it is a process likely to progress irregularly in these multiple domains. However, the process is well underway and is gathering speed, and if the FDA neglects this process, it will be at our peril. This confronts the Agency with rapidly emerging need to absorb, manipulate, assess and interpret new kinds of information and to relate them to likely drug action. Increasingly, the Agency may be asked to approve stratified application of new drugs, biologicals and devices coupled with genomic and biochemical testing. Indeed, the increased marketing of such testing directly to the consumer is likely only to increase and may demand continuous regulatory evaluation. This, in turn, will have an even larger impact on medicine than did the digitalization of information technologies on the field of communications. The new medicine will require similarly significant advances in information technology and informatics to support novel

data and information needs that are arising from rapidly evolving new sciences and their exciting applications.

These same systems changes will come to all areas of biology relevant to the FDA — agriculture, food, nutrition, toxic environmental responses, etc. Furthermore, many other emerging sciences are rapidly evolving and contributing to the complexity of the paradigm. The rapidity with which these sciences materialize may be debatable, but few doubt that they will become a reality. Products based on these related areas of science are already in development.

FDA must not only act now to catch up with the new knowledge and technology available today, but the Agency must have the strength in science and information to anticipate and respond to as-yet unidentified challenges. FDA has taken two important steps to accomplish this: 1) launch in 2004 of the Critical Path Initiative[21]; and 2) assessment of its drug safety program to ensure the program is the best possible based on application of new scientific tools. Some groups have referred to the Critical Path Initiative as a vision that if implemented will "transform the FDA from an organization of rule-based regulators to a public health Agency staffed with 21st Century science-based standard setters[22]." Despite its predicted impact on safety and reduction in the time and cost of development of new life-saving products, the initiative, for lack of funds, has only begun to be implemented. FDA asked the Institute of Medicine (IOM) to convene a committee to assess its drug safety system. The resulting report[23] makes substantive recommendations for improvement. However, implementation requires application of new scientific and bioinformatics tools and extensive external collaborations to gain access to the necessary scientific expertise and databases.

FDA reviewers and their decisions will be poorly informed, the potential to dramatically improve drug development and safety will go unrealized, and the public health will be poorly served without the personnel and funds to fully develop and implement the Critical Path Initiative and the IOM recommendations. It is for this reason that the Subcommittee spent considerable time reviewing progress to date on both the Critical Path Initiative and the IOM report, as well as the current status of genomics and bioinformatics, which provide the underpinnings of both.

[21] In March 2004, the FDA released a white paper entitled *Innovation or Stagnation?: Challenge and Opportunity on the Critical Path to New Medical Products*. This report is often termed the "Critical Path Initiative." *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products* [Online]. Available at http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html

[22] *A Working Paper of the 21st Century FDA Task Force*, June 2006, at http://www.manhattan-institute.org/html/fda_task_1.htm#01

[23] IOM (Institute of Medicine) 2007. The Future of Drug Safety: Promoting and Protecting the Health of the Public. Washington, DC: The National Academies Press.

Finally, the Subcommittee notes that the public is understandably confused by the growing disconnect between the promises of cutting-edge science and the reality of clinical benefit. Traditionally, they have looked to the FDA for guidance in this regard, as the purveyor of a seal of approval to the quality of care that they seek. Thus the FDA must play a critical role in translating the quality of innovation to health care professionals and the public at large. This remit must rely primarily on the emerging science of benefit: risk communication, whereby the public is made to understand the trade-offs involved in accepting newer therapies. FDA must be encouraged to play a leadership role in this form of communication[24][25]. This serves to illustrate once again the need for FDA to have leading-edge scientists who can contribute to this important role for FDA.

[24] See Slater, Eve. Today's FDA. NEJM.352:293-297.2005

[25] Mussen, F., Salek, S., Walker, S. A Quantitative Approach to Benefit-Risk Assessment of Medicines; Part 1: The Development of a New Model Using Multi-Criteria Decision Analysis; Part 2: The Practical Application of a New Model. Pharmacoepidemiolgy and Drug Safety. In Press. 2007

Section 3

Discussion of Key Findings and Recommendations

3.1 Science: Capability, Capacity and Organization

As part of our review, the Subcommittee asked that FDA: 1) provide an enterprise-wide outline of core regulatory activities that FDA must undertake to discharge its statutory responsibilities and that must be informed and supported by modern science, 2) identify opportunities for modernizing regulatory science at FDA, and 3) identify technology and current scientific limitations mapped to these core regulatory functions[26]. The Subcommittee also did its own assessment by interviewing staff, reviewing previous assessments by the FDA Science Board and the Institute of Medicine of the National Academy of Sciences, and evaluating publicly available written materials provided by FDA to the Subcommittee. The Subcommittee also conducted selective interviews of major stakeholders.

The Subcommittee was impressed with the expertise and high level of professional and personal commitment of many of FDA's science staff. In some cases, science programs and activities have been developed and have achieved important mission-fulfilling results predominantly because of the extraordinary commitment of staff to the FDA mission, despite inadequate resources, organizational structure and formal capacity. But despite this commendable commitment of staff, we found that scientific capabilities and capacity at the FDA overall are unevenly meeting current requirements, have areas of serious deficiencies and are not positioned to meet future needs. Most of these deficiencies are the result of the dramatic increase in responsibilities of the FDA on the one hand and the lack of increasing personnel and scientific expertise to fulfill these responsibilities on the other. Although this is the case for all Centers, the ones responsible for food safety, CFSAN and CVM, have been most adversely affected. In particular, we noted that few scientists at the FDA have the leading-edge expertise that will be so essential for managing the rapidly changing face of diagnostics and therapeutics in the emerging 21st Century world of genomics and systems biology.

Regardless of resources and personnel, for science at the FDA to be effective in supporting its mission, the FDA must have 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. It should identify the areas of regulatory research needed to fulfill its mission but cannot be conducted outside the Agency. The

[26] See Appendix L, *Task 1: Outline of Core FDA Regulatory Functions*

vision should delineate the role of science in determining how FDA effectively responds to new technologies and facilitates the introduction of those technologies to consumers in a safe and effective manner.

A consistent theme the Subcommittee observed through virtually all of our discussions with staff and in subsequent Subcommittee deliberations is the absence of an Agency-wide vision for the role of science, the importance of leading-edge skills in science, priorities for the science program, coordinated maximization of science resources, oversight of program performance, and an infrastructure to act on this vision. Scientific leadership at the Center level is variable. In some cases it is outstanding: for example, CBER has a rigorous process for establishing priorities and the impact of Center research on regulation. In addition, the leadership of CBER insists upon integration of laboratory scientists both in the review and manufacturing site inspection processes. External peer review of research programs is the norm rather than the exception. However, there is a lack of consistency across the Agency, resulting in missed opportunities for leveraging expertise and resources and identification of areas in need of greatest attention.

3.1.1 Finding: FDA does not have the capacity to ensure the safety of food for the nation.

Recommendation: Rebuild CFSAN, CVM scientific base and their related inspection and enforcement functions to a level that is commensurate with their regulatory responsibilities.

The Subcommittee found that FDA's ability to provide its basic food system inspection, enforcement and rulemaking functions is severely eroded, as is its ability to respond to outbreaks in a timely manner and to develop and keep pace with the new regulatory science needed to prevent future problems arising from both novel (prion disease, genetically modified organism) and traditional (resistant microbes, chemical contamination) sources. There is an appallingly low inspection rate: the FDA cannot sufficiently monitor either the tremendous volume of products manufactured domestically or the exponential growth of imported products[27]. During the past 35 years, the decrease in FDA funding for inspection of our food supply has forced FDA to impose a 78 percent reduction in food inspections, at a time when the food industry has been rapidly expanding and food importation has exponentially increased. FDA estimates that, at most, it inspects food manufacturers once every 10 years, and cosmetic manufacturers even less frequently. The Agency conducts no inspections of retail food establishments or of food-producing farms.

[27] See Appendix B, *The State of Science at the Food and Drug Administration*

There are several reasons for the crisis in CFSAN and CVM. One is a dramatic increase in and diversification of Agency responsibilities, reflecting the sharp increase in FDA regulatory mandates and the challenges of globalization. Another is the increasing complexity of the task: surveillance combined with the complexities of cross-Agency regulatory responsibilities and a general lack of coordination across agencies. A third is the increased scientific demands placed on the Agency due to the emerging sciences that are resulting in new products for humans and animals. Finally, a recurrent theme — that of inadequate resources. In this case, inadequate sensing technology to augment surveillance and investigational activities, inadequate scientific capability to effectively model food supply risks, and inadequate staff to inspect an adequate sample of domestic and internationally produced food products all limit the effectiveness of the Agency.

The Subcommittee's findings are consistent with those of previous committees that voiced deep concerns about the viability of the foods program and the lack of Agency priority for food issues. Sixteen years ago the Final Report of the Advisory Committee on the Food and Drug Administration to the Secretary of Health and Human Services (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." Since 1991, continued declines in resources and personnel have exacerbated this situation.

CVM has the authority of ensuring the safety of milk, meat and eggs. However, the Center is faced with myriad other regulatory demands; including assessing safety of genetically modified foods and engineered animals used to make biotechnology-based drugs for humans (so-called biopharming); developing analytical techniques to screen meat, milk and eggs for volatile residues of drugs, pesticides and environmental contaminants; as well as managing the approval of an explosion of new pet-animal drugs that are essentially a microcosm of the human drugs regulated by both CDER and CBER (partially supported by Animal Drug Use Fee Act). When Bovine Spongiform Encephalopathy (BSE), commonly known as mad cow disease, first appeared in Europe and elsewhere, consumers and the industry looked to the FDA to ensure that the disease would not spread to the US through the animal feed that FDA regulates. But Agency officials were denied the funds to bring the feed industry into rapid compliance with the new feed regulations, and the disease did indeed appear in the US. Perhaps if the small sums requested by FDA had been provided, Japan and other countries would not have cut off imports of US beef and American producers would not have suffered multibillion dollar losses. To this day, the BSE research program, as well as others in the CVM

related to detection of newly emerging infectious agents, remains seriously underfunded.

The recent pet food safety crisis has strained this overtaxed system. CVM received more than 18,000 telephone calls concerning melamine pet food contamination. The pet food industry is a $15 to $20 billion a year business and largely 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 is able to devote only two people working full time on pet food issues.

It is crucial that both food-based Centers develop the science needed to fulfill their mandated missions. The strengthening of science in these Centers must be insulated from acute crisis management. This will involve a two-pronged approach. The first is to immediately correct the historical lack of support for staff and infrastructure needed to address current issues. Both Centers have accurately defined areas that need attention, and this Subcommittee agrees with this assessment. Directly supporting these initiatives is largely one of funding, as addressed in recommendation 1[28].

The second phase is to significantly build a 21st Century science-based regulatory science that could anticipate future food safety issues and develop a cadre of professionals capable of applying the new biology, chemistry and bioinformatics to the regulation of foods that exist in the manufacturing, distribution and consumer use environment of today's global marketplace. A culture must be created in which such individuals have the freedom and support to pursue the regulatory science needed to keep pace with a global economy using the tools provided by a new biology. These individuals must be isolated from acute regulatory crises.

The Subcommittee recommends that CFSAN and CVM leverage other research programs (e.g., National Center for Toxicology Research [NCTR], the Agricultural Research Service [ARS], Cooperative State Research, Education and Extension Service [CSREES], Centers for Disease Control and Prevention [CDC], National Institutes of Health [NIH] and Department of Homeland Security [DHS]) research programs to address food and cosmetic safety priorities in toxicology, microbiology, human and animal nutrition, and issues of emerging science. However, due to the unique regulatory landscape of products managed by both CFSAN and CVM, internal up-to-date scientific expertise is mandatory. CFSAN and CVM need to have resources that can be brought to the partnership and that could be used to fund joint requests for proposals managed through granting agencies. One very successful example of such joint programs is the Plant Genome Initiative, funded by National Science Foundation (NSF), Department of Energy (DOE) and US Department of Agriculture (USDA) and managed by NSF.

[28] See Appendix C, *Center for Food Safety and Applied Nutrition (CFSAN)*

This second phase should be conducted in parallel with this Subcommittee's recommendations for Agency-wide changes in science administration and support as embodied in a Chief Scientific Officer with budgetary authority, as well as modernization of IT infrastructure. The unending series of *management by crisis* in both CFSAN and CVM has seriously eroded the morale of existing dedicated staff and hampered recruitment of new scientists trained in areas of emerging biology, chemistry and bioinformatics. This situation, coupled with the early retirement of senior scientists and the recent departure of the director of CFSAN, puts the state of science in serious disarray. These issues should be a high priority on the agenda of the new Chief Scientific Officer.

Finally, efforts to strengthen the food safety mission of FDA must not adversely affect CFSAN's legislatively mandated mission to address the science behind nutrition, and the safety of dietary supplements and cosmetic safety. In fact, these areas must be revitalized and prioritized independently of both food and drug issues to redress decades of neglect before a serious crisis emerges[29]. The dietary supplement industry has grown to more than $20 billion in annual sales, and millions of Americans use those products every day. But the legislation authorizing FDA regulation of those products has never been funded, the practical effect being that the products and their health claims go essentially unregulated. The same can be said of the cosmetics industry, which has more than $60 billion in annual sales, but is overseen by an FDA staff of 14 supported by $3.5 million budget. This industry is rapidly integrating nanotechnology for product delivery and yet, very limited expertise in this newly emerging area of science exists in the entire FDA.

3.1.2 Finding: The development of medical products based on "new science" cannot be adequately regulated by the FDA.

Recommendation: The FDA must develop a program to manage "new science" that will provide a standardized approach to enable the FDA to address all emerging sciences and technologies.

Rapid changes in biological sciences and bioinformatics are exceeding the capacity of current FDA science capabilities to keep pace and adequately support the Agency's safety mission. The FDA lacks sufficient expertise to understand the impact of product use, to maintain ongoing currency with their evolution or to evaluate the sophisticated products produced. In addition, the FDA has no consistent strategy to acquire that expertise. No process or mechanism

[29] See Appendix C, *Center for Food Safety and Applied Nutrition (CFSAN)*

exists to link the work of key groups in areas of emerging science, such as genomics, metabolomics and proteomics, to larger Agency science or regulatory goals or priorities.

The lack of prioritization associated with areas of emerging science is also a major challenge. More than 70 items were listed as high-priority areas of focus in the Critical Path Initiative, without further prioritization. We could find no indication that efforts regarding other areas of emerging science that will impact the Agency's mission are in a more advanced stage than genomics. And genomics is in only the rudimentary stages of development. The Subcommittee found there has been a serious commitment in sustaining momentum for the Critical Path Initiative, primarily due to heroic efforts by several senior FDA administrators. However, even though there is a great deal of enthusiasm, many Critical Path projects and pilots that have been initiated are currently at risk. None is adequately resourced. Although some remarkable successes have been emulated internationally, most have stagnated[30]. The Initiative has been limited by a significant lack of resources for maintaining operations, let alone adding the trained professionals necessary to bring the Critical Path strategy to tactical reality.

The Critical Path Initiative in certain areas pursues an ambitious agenda. However, the initiative should be expanded into a more comprehensive activity that addresses all regulatory activities at the FDA, as well as all aspects of the regulatory life cycle for each category of regulated product. For example, although the Initiative has expanded during the past two years to include all regulated products (e.g., foods, cosmetics and veterinary products), the current Critical Path Initiative does not include pharmacovigilance. Finally, the Critical Path Initiative remains a promising foundation even within the scope of its current mandate since it has yet to receive the resources it needs to manage the onslaught of innovation among medical and food products. If the FDA is to achieve its regulatory mission, it must support a complete and integrated life-cycle approach from pre-market development to post-market surveillance. (The Subcommittee notes that product quality is also important to regulated products across the Agency.) The Subcommittee recommends that the Agency establish new organizational mechanisms and target additional resources to implement the Critical Path Initiative fully, and that the Critical Path initiative be expanded to include all regulated products and their associated life cycles.

The lack of an adequate IT infrastructure creates further challenges. Against the backdrop of an already inadequate information system across the Agency, as discussed in our additional findings below, there is minimal genomics IT infrastructure to support genomics-focused efforts. This is an especially important deficiency because genomics as well as proteomics, metabolomics, combination products (drug or

[30] See Appendix E, Center for Drug Evaluation and Research (CDER)

biologic and a device) and other emerging sciences and technologies are creating larger amounts of data than current technologies in support of product design, testing, and production and for ongoing safety analysis[31].

The lack of new science capability/capacity places the FDA mission at risk for those many products at the leading edge of innovation. This compromises not only the public health mission since the Agency cannot effectively regulate products built on emerging science, but it also hamstrings the Agency's ability to support innovation in the industries and markets that it regulates. The Subcommittee identified the following eight emerging science and technologies that are most challenging the FDA: systems biology (including panomics), wireless healthcare devices, nanotechnology, medical imaging, robotics, cell- and tissue-based products, regenerative medicine, and combination products. Each of these emerging areas is developing at an exponential rate and each generates novel scientific, analytic, laboratory and/or information requirements.

The area of genomics serves to illustrate many of these points. Several of the genomic technologies are currently impacting critical regulatory issues, such as evaluation of benefit/risk, drug and vaccine safety, and new drug target identification. At the present time the capability to analyze submitted data is strained by lack of expertise, lack of adequate IT and bioinformatics systems, and difficulty in integrating science directly and seamlessly into the reviews. The extremely successful Voluntary Genomic Data Submissions (VGDSs), now expanded to VXDS to cover additional technologies, depends on heroic efforts of senior administrators and scientists in essentially an *ad hoc* program.

With regard to efficacy issues, the FDA is receiving growing numbers of sponsored programs where the use of genetics and genome-wide association analyses may separate and identify patients with genetic profiles who are more likely to experience an intended effect of the drug candidate (efficacy pharmacogenetics, personalized medicine). These analyses cannot currently be adequately reviewed without extensive *ad hoc* external collaborations involving bioinformatics, genetic, and medical genetics expertise, which are currently not adequately represented within the FDA. The mission of getting safe and effective drugs to patients in a timely manner is currently threatened by inadequate expertise and capabilities. Drug target identification using genome-wide association also requires expertise for understanding the science and mechanisms of increasing numbers of new molecules submitted to the FDA for review.

The area of drug safety now has several examples that favorably affect the benefit/risk ratio. Safety pharmacogenetics using genetic technologies can, and have, defined "diagnostic" profiles that can

[31] See Appendix E, *Center for Drug Evaluation and Research (CDER)*; Appendix I, *Genomics*; and Appendix K, *Information Technology (IT)*

predict which patients should not risk an adverse event before they take the drug. The Subcommittee stressed the importance of safety science. For one recent example, where there is a potentially severe allergic hypersensitivity syndrome response to an HIV medicine — which is otherwise relative safe — a sponsor has developed and validated a genetic test that can identify patients at risk of the allergic response with >97 percent accuracy. The use of this test clearly reduces the drug risk for this particular drug, but also affects the clinical benefit/risk relationships of other approved and available drugs and drug candidates. The test reduces the rate of allergic reactions in people on multiple drug regiments and thus avoids the possible inappropriate discontinuation of important therapeutics due to confusion about the offending allergen. This is not simply "new science," but represents the coming wave of "new medicine" and the need for "new regulatory scientists."

The Subcommittee recommends that the FDA create a cross-Agency effort that will include the following:

- An overarching governance structure to provide a forum for constant scanning of the environment for "new sciences" (so the Agency will not have to play "catch up" as they are now doing with genomics) and the ability to direct resources to build capacity in a "new science"
- The creation of working groups that will evaluate, develop strategy and reduce to practice a cross-Agency collaborative approach to a "new science" to ensure that the FDA has the scientific and information processing expertise to regulate products based on new sciences
- The establishment of ongoing extramural collaborations with other agencies, academia and industry to ensure that new sciences are identified and that innovations are understood by FDA science and regulatory staff

The FDA must have the ability to manage a portfolio of "new science" that includes innovation life-cycle management. "New sciences" will mature and be released from the "new science" portfolio of the FDA once a specific scientific domain reaches a certain level of maturity and it is clear that the FDA has sufficient expertise and resources to expertly regulate products derived from that domain.

The Subcommittee specifically recommends that this integrative, cross-disciplinary entity to manage a portfolio of "new sciences" should have at least 20 research scientists and their support colleagues. The sole mission of this new entity would be to delineate the tools and approaches that will be necessary to manage the tremendous innovation that is impacting the FDA as well as the impact of change due to complex systems in biology, technology, commerce and social networks that also inform the regulatory mandate. The committee notes that in order to lead and realize the enormous opportunities

arising from innovation across numerous scientific fields that are simultaneously informing the development of new products, the Agency must have scientists who understand, embrace and can practice the essential cross-disciplinary domains of science, technology, business and policy to release the potential of emerging innovation while ensuring appropriate safety and efficacy profiles of new products.

The new entity, which could be called the **Incubator for Innovation in Regulatory and Information Science (IIRIS)**, would be under the direction of the Chief Scientific Officer and would invest in the recruitment of talented cross-disciplinary scientists to serve as liaisons with groups across the Agency involved in the "new science" programs. The IIRIS team would not do the scientific work, but rather would be the project managers to nurture and track program progress. IIRIS would also be responsible for the creation of the proper computation, technical and biological infrastructures (e.g., measurement, visualization and computational facilities), and work closely with the Director of External Collaborations and Training to create strategic partnerships with academia, industry and governmental laboratories to deliver the competency necessary in science, technology, commerce and policy to support industry innovation and the delivery of safe and efficacious products to the marketplace.

IIRIS would be intimately involved in establishing the overall scientific strategy of the FDA and in development of annual budgets to accommodate the "new sciences portfolio." IIRIS would provide the ideal mechanism for FDA interactions with the recently established Reagan-Udall Foundation[32], the purpose of which is to advance the mission of the FDA to modernize medical product development, accelerate innovation and enhance product safety.

In particular, the need to accumulate the intramural expertise and the extramural collaborations necessary for IIRIS to pursue its mission outstrip substantially the budget projected for the Reagan-Udall Foundation. A particular opportunity for the FDA will be to harness the substantial potential of the academic sector where many of the innovations and early applications of emerging technologies are likely to occur. However, this will require deployment of sufficient resources to align the interest of such academic centers of innovation with those of the FDA. In this regard, the lesson of the Critical Path Initiative is salutatory. Inadequate provision of resources undermined the ability of the Agency to engage the leading centers of innovation in the emerging sciences in this initiative. Given the speed of technological change, the relevance of the new sciences to drug development and risk management and the need for the intramural scientists in IIRIS to interact with extramural collaborators, it is vital that IIRIS be adequately resourced.

[32] Reagan-Udall Foundation (Title IV) is a not-for-profit corporation, separate from the federal government, whose purpose is to advance the mission of safety.

It is critical that FDA have a group of outstanding scientists to help identify, prioritize and make recommendations to the Foundation, but also to play the same role within FDA for areas that may not be pursued in the Foundation. The Foundation is charged with identifying "unmet needs in the development, manufacture and evaluation of the safety and effectiveness" of drugs, biologics and devices, including post-approval safety. It will be equally important to have a strong internal FDA group whose responsibility it is to implement and integrate new findings generated by the work of the Foundation. IIRIS should be positioned to do this.

The success of IIRIS will depend on recruitment of the most outstanding scientists on the cutting edge of those areas selected for the "new sciences" portfolio, as well as carefully constructed governance activities to establish the optimal balance between basic research and applied regulatory science as well as priority topics. It would not be technically feasible, nor economically advisable, for the FDA to establish comprehensive "new science" programs internally. Rather, a "new science" program would be constituted of a small nucleus of experts that could interact with external centers of scientific excellence.

It is proposed that the intramural scientists would be one "hub" in a consortium linking the FDA with extramural "hubs" within IIRIS. Such a consortium would greatly expand the reach and expertise of the Agency and release the potential within the academic sector to contribute even more effectively to the national effort to develop innovative, safe and effective medicines. Different "hubs" in this network might have distinct, but complimentary areas of expertise in the "new sciences." Topics pursued in several of these might include, but not be limited to:

- Systems Biology and Medicine: This would be the logical first "new science" program in the portfolio and would include expertise in genomics because of its enormous impact across the Agency's regulatory responsibilities (includes in food safety-product monitoring for infectious agents, livestock (mad cow), and tracking of food sources and in drug safety-creative use of genome-based technologies in drug approval applications such as patient identification and disease stratification, pre- and post-clinical safety measurements, drug responsiveness (biomarkers), and post-launch safety/utility) and because of its current vulnerable state within the Agency[33]. However, it would also include expertise in proteomics, metabolomics, new measurement and visualization technologies and the necessary computational and mathematical tools to acquire, store, validate, assess, integrate and extract the informational essence from the increasingly large and complex diverse datasets that will inundate the Agency. Moreover, the emergence of systems biology that

[33] See Appendix E, *Center for Drug Evaluation and Research (CDER)* and Appendix I, *Genomics*

integrates together genomics, proteomics and the other omics, new technologies (nanotechnology and molecular imaging) and powerful computational tools provides a special opportunity for doing more for less — if the right people can be recruited and the supporting infrastructure created.

- Translational Medicine and Therapeutics: A radical "new science" program within IIRIS that impacts drug development in a way that is just as revolutionary as the changes that have occurred in drug discovery. The new science should have the capacity to: 1) develop and project mechanism-based quantitative biomarkers from model systems to humans, 2) evoke phenotypic responses in humans to guide individualization in rational dose selection, and 3) harness unbiased technologies to select among molecules directed against a single target.
- Other examples of areas of expertise pursued extramurally within IIRIS might include other areas of emerging science identified as high priorities by the Subcommittee: 1) innovative approaches to imaging drug response, 2) nanotechnology and targeted therapeutics, 3) novel therapeutic modalities (stem cell, gene, tissue therapeutics), and 4) innovative data acquisition and trial design.

The development of this network within IIRIS might be viewed as the creation of a "Jet Propulsion Laboratory" for the FDA — harnessing the expertise of a broad extramural community to afford a testing laboratory where ideas emanating from IIRIS investigators within or outside the FDA might be pursued rapidly and efficiently to integrate the emerging sciences with the regulatory mission and through educational initiatives to increase the pool of those with expertise in the regulatory sciences of the 21st Century. This partnership could also leverage the NIH Clinical and Translations Science Awards and existing FDA investments in education and informatics. It should also leverage partnerships with industry as long as potential conflicts of interest are recognized and managed.

3.1.3 Finding: There is insufficient capacity in modeling, risk assessment and analysis.

Recommendation: The FDA should immediately implement the IOM recommendations for improving drug safety, as well as those made by the Subcommittee working group on Surveillance/Biostatistics.

The Subcommittee reviewed statistical science across the Agency. We also reviewed the IOM report[34], which places a strong emphasis on the

[34] IOM (Institute of Medicine) 2007. The Future of Drug Safety: Promoting and Protecting the Health of the Public. Washington, DC: The National Academies Press.

application of the emerging science of safety, met with the senior author of the report, and requested a briefing on FDA's response to the report. We concur with the IOM's findings of scientific gaps in surveillance and biostatistics, and are in substantial agreement with the IOM recommendations directed to the Agency and with FDA's proposed response. We note that implementation will be driven by having the required expertise in new areas of science and development of appropriate methods, and that extensive collaborations with academia, industry and other government agencies will be of paramount importance.

Our findings and recommendations of highest priority are summarized below. Although there are many needs (e.g., external collaborations and IT support) in all Centers and programs, none is as time sensitive and critical as surveillance and risk management.

The Subcommittee found that there is an urgent need for developing and evaluating new statistical methods that are most appropriate for the data generated by new areas of science. The Subcommittee notes that new challenges are posed by the wealth of new types of data arising from animal studies, early clinical work and new approaches to safety surveillance.

The Subcommittee recommends that statisticians help develop and issue guidance on the interpretation and application to product development of data from new sources, e.g., methods to evaluate and appropriately interpret data from microarray and systems biology experiments. New statistical approaches will also be needed to address the deluge of data on product safety that will become available electronically from networks of care providers, including government agencies such as Centers for Medicare and Medicaid (CMS) and the Veterans Administration (VA). The initial work on data mining techniques has been promising, but continuing work in this area is essential if optimal use is to be made of these data. Statistical and epidemiological expertise will need to be brought to bear on the most efficient and productive analytical approaches to identifying and evaluating signals arising from such databases. FDA will also need new methods for other areas of emerging science, such as surveillance for emerging infectious diseases relative to food safety.

The Subcommittee found that the FDA lacks sufficient expertise in quantitative methods, such as statistics and biomathematics, to effectively assess products and guide sponsors to design valid and informative studies.

The Subcommittee recommends that statisticians be engaged in developing new, potentially more efficient designs to evaluate new products, especially those that may offer substantial improvements in treating and/or preventing disease. It is critical for the FDA to develop expertise in these areas, particularly focusing on targeted designs (often including validation of assays for the target) for new drugs aimed at individuals with specific genomic characteristics, use of

Bayesian methods to supplement standard methods and increase understanding of study data, and approaches to the design and analysis of studies involving bioimaging, microarray and proteomic experiments as well as methods for other areas of emerging science.

The Subcommittee found that the FDA also has a lack of expertise in risk/benefit assessment. The Subcommittee notes that another important area for quantitative methods development is risk-benefit assessment. Such assessments have traditionally been made informally, but as the public's concern about the value and safety of new drugs continue to grow and as the complexity and volume of data informative about potential benefits and risks increases, more formal methods will be important for optimal decision making.

The Subcommittee recommends that the FDA develop increased awareness of and expertise in design and analytical methods to conduct quantitatively and semi-quantitative risk benefit analyses. Further, the Agency should develop a framework through a transparent and public process for use of such analyses in regulatory decision making.

The Subcommittee recommends that the FDA strengthen the information tools for supporting effective risk assessment. This would provide the FDA with improved capacity to identify safety risks in advance and to conduct effective risk assessment, analysis and communications. Key areas of focus would include providing improved database access and analysis in support of safety assessment, including access to health and public health databases for adverse-event identification and surveillance for risk identification and evaluation. It would also include the development of advanced data mining and analytical methodologies for signal detection in large health care databases. The FDA should also focus on the development of risk-based models for planning and conducting manufacturing inspections, and invest in risk communications science.

The FDA could, in part, achieve these recommendations by:

- Offering regular interdisciplinary training to senior scientific staff in areas of emerging science to optimize regulatory decision-making
- Developing ways to measure and disseminate information on "real-world" benefits and risks using large clinical datasets
- Developing and evaluating study designs for targeted therapies that may facilitate adoption of personalized drug treatment
- Developing and evaluating new statistical methods and trial designs with the potential to increase the efficiency of drug development

The FDA should also expand the drug safety framework to apply "active surveillance" to medical devices, animal drugs and possibly foods, as well as human drugs and biologics. This would at a minimum

include providing access to existing databases with relevant medical information to FDA reviewers. It should increase the level of staff expertise in scientifically based risk communication strategies and increase the involvement of external stakeholders in evaluation of FDA approaches and processes.

The Subcommittee also urges the FDA to develop enhanced reviewer tools, such as data standards, electronic submissions, data mining and analysis as well as tools for electronic facilities, establishment, and product listing and tracking.

3.1.4 Finding: The FDA science agenda lacks a coherent structure and vision, as well as effective coordination and prioritization.

Recommendation: The FDA should institute a new scientific organization.

The Subcommittee believes rapid and careful centralization of the science program is essential to enable science to appropriately inform the regulatory process. The importance of centralization and its urgency results from the convergence of several influences of significance in their own right, including the rapid changes in important areas of science relevant to the Agency's mission, science resource shortages, challenges in important areas of science expertise, and increasing need for multidisciplinary, even interdisciplinary approaches.

During the course of the Subcommittee's work, the Commissioner created the role of "Deputy Commissioner/Chief Medical Officer," who will be responsible for planning, executing and monitoring FDA scientific and medical projects. This newly created position and the Office of Scientific and Medical Programs will be responsible for the Critical Path Initiative, the FDA Fellowship Program, and performance of scientific research on the safety of regulated products through the National Center for Toxicological Research. There is a unique opportunity to strengthen the scientific infrastructure at FDA with the establishment of this new position and the opening of the new White Oak campus, which should facilitate consolidation of the research laboratories of CDER, CBER and CDRH.

Despite the Agency's focus on transactional issues and structured around formal processes, and despite the naming of a Deputy Commissioner, we believe much more is needed to achieve the required level and effectiveness of central leadership and direction for the science program. Successful central direction requires clarity of and experience in establishing and overseeing enterprise-wide policies, goals, standards, oversight and accountability for large complex science-based organizations. Success also requires sufficient empowerment, infrastructure and resources to bind the centers and other functional areas to a common vision and set of expectations

regarding the role of science, its management, prioritization of effort and optimal use of science resources.

The centralization required is not simply one that comes from a senior person being on point. What is needed is a broadly empowered leader exclusively charged with managing and advocating for the science program. Also needed is a nimble infrastructure that can efficiently support central management aligned with Agency priorities and enabled by cross-Center engagement.

The Subcommittee recommends in *the strongest way*, the creation of such a central science infrastructure for developing, implementing and ensuring the execution of an effective science program. The following recommendations are critical: strengthen the role of the Deputy Commissioner/Chief Medical Officer. Appointment of a Deputy Commissioner to be responsible for all scientific aspects of FDA is certainly a big step. However, it seems that responsibility for all medical and scientific aspects of the Agency might be too much for a single individual, given the significant rebuilding required to strengthen the scientific base of the Agency. The Subcommittee feels that, ideally, there should be two separate Deputy Commissioners. If this is not feasible, then at a minimum, the title of the newly created position should be changed from Deputy Commissioner/Chief Medical Officer to reflect an equally important role of scientific leadership in this position, namely to Deputy Commissioner of Medical and Scientific Affairs. This individual should ensure that an Agency-wide science program is aligned with the Agency's mission, goals and priorities. This individual should be provided with sufficient budget to:

- Support program development, implementation and oversight
- Have the authority to develop, implement and oversee all science activities at the Agency, including budgetary authority
- Co-ordinate the science activities of individual centers with Agency-wide programs and goals
- Ensure the adequacy of science expertise across the Agency through effective recruitment, retention, ongoing professional development, and external partnering and collaboration

- Create an interface between regulators, industry and other federal agencies. This will permit access to the best science and allow the Deputy Commissioner to champion FDA transformation and adoption of validated new science, such as biomarkers, as well as coordinate related Agency activities. Validated new science can then be deployed into every stage of the regulatory review for all regulated products.
- Locate the office within the Office of the Commissioner and position it to ensure direct participation in senior leadership deliberations on Agency priority and goal setting, formulate and defend the annual science budget request. The officer should have

direct access to the Commissioner and Science Board on matters of science priorities, program and resources.

The Subcommittee recommends the establishment of the position of a Chief Scientific Officer. The Amendments Act of 2007 directs the Secretary to appoint such a position. This officer should report directly to the Deputy Commissioner. The selected individual should have an exceptional record of research accomplishment based on publications and national/international reputation in "cutting-edge" research relevant to FDA, such as translational medicine and therapeutics, systems biology, new high-throughput technologies and their applications, computational data analysis and interpretation. The individual should have experience in science administration, operations and financial management, and, ideally, will be experienced in managing multi-institutional collaborations, have superb organizational and teambuilding skills, and a have a commitment to working with a group of highly motivated scientists. The individual should be charged with developing a transparent process of strategic planning and priority-setting, and providing scientific leadership and management oversight of science. The individual should also be charged with overseeing the recruitment of all scientific research personnel, in consultation with the Center directors.

The Subcommittee recommends that a new position, that of Deputy Director for Science, be created within each Center. Each Deputy Director should have dual reporting responsibilities: to the Center Director and the Chief Scientific Officer. Each individual should be responsible for organizing and managing science within the Center consistent with Agency science priorities and Center needs. The individual should have the vision necessary to direct a highly skilled team of researchers, clinicians, support staff and trainees, creating and delivering a wide-ranging program of fundamental, enabling, and translational applied research within the mission of FDA. The individual should be an experienced research group leader with an established track record of accomplishments in "cutting-edge" science relevant to the Center and commitment to the collaborative ethos that underpins effective multidisciplinary research activities.

The Subcommittee recommends that a new position, that of Director of Extramural Collaborations and Training, be created. This individual would jointly report to the Deputy Commissioner and the Chief Scientific Officer and serve as a principal advisor on scientific affairs affecting the extramural community. The individual should have had extensive experience in interacting with the scientific community and have a track record in strong collaborative research projects with investigative teams from multiple institutions. The new Director would develop and recommend procedures and policy for the execution of collaborations; determine effectiveness of current programs and recommend new programs in order to meet the Agency's needs, lead staff and develop collaborations and relationships with other agencies and also with science-based advocacy groups and industry, and

establish robust training program and visiting scholar program as specified in Section 3.2, *Workforce: Securing Critical Scientific Capability and Capacity*.

The Subcommittee recommends that a Board of External Scientific Counselors (BESC) be created for each Center. The Board would:

- Comprise outstanding representatives from industry, academia and other relevant agencies, including NIH, CDC and USDA
- Meet a minimum of three times a year
- Be involved in review of research programs and establishment of policies.

The Chairs of the BESCs would make up a standing Advisory Committee to the Chief Scientific Officer. The BESCs should be charged with providing ongoing review of the processes of quality control across FDA. The Chair of the Boards would be ex-officio members of the Science Board.

To improve quality review, the Chairs and members of the BESCs should be appointed by a process to ensure expert, arms-length membership; that the process by which the BESCs review the Centers be explicit and consistent; and that the criteria used to evaluate scientists and reviewers be made more rigorous.

The main role of the Boards would be to provide rigorous, ongoing review of science within the Centers. There appears to have only been two other external reviews of the Agency as a whole with particular emphasis upon science. While individual programs within Centers have been externally reviewed and some aspects of Centers have been reviewed by the FDA Science Board, the reviews of entire Centers including priorities, research programs, processes, scientific expertise, resources, strategic plans, etc., are reviewed inconsistently and, at best, only every four years. According to what the Subcommittee could determine CDER and the Office of Regulatory affairs have never been externally reviewed; rather, individual programs have been reviewed as a result of an apparent crisis.

Regular external review of Centers and public sharing of data would facilitate proactive planning and would broaden awareness of resource constraints and the potential impact on public health. It should also lead to consistency across the Agency and establishment of best practices if the results are shared with Center Directors and other Agency leadership. Furthermore, it would also serve the important purpose of helping to educate the public and the stakeholders. Finally, an important goal of ongoing external peer review would be to determine the relevance of the FDA intramural and extramural research activities to the regulatory mission of the Agency and the quality of review used in awarding extramural funding.

An annual, prospective planning process should be conducted by each Center to determine the allocation of resources to the research programs. The process should be outlined in a written document and reviewed and approved, and monitored by the Science Director of the Center, Chief Scientific Officer, BESC, IIRIS, FDA Commissioner and the FDA Science Board. Extensive consultation with extramural scientists in industry, academia, and other relevant government agencies should be part of this process. The overall FDA research mission should be assessed and allocation decisions made on the basis of scientific excellence, priority, and opportunity. The BESC should, in a public session, annually review these needs vs. budget, organization, infrastructure and results achieved to support Agency science.

On an ongoing basis, the Board should also provide assistance in identifying and prioritizing needed science staff expertise, such as scaling staff capacity for key areas of expertise; identifying effective, relevant recruitment and retention strategies in industry and academia; and identifying areas of science that would potentially provide high value for external partnering and collaboration.

The Subcommittee identified three areas that need further review and attention by the FDA Science Board:

- NCTR
- Office of Regulatory Affairs
- Potential minority health disparities

The Subcommittee recommends that a rigorous external and internal review of NCTR be conducted in order better to integrate research expertise and services into other centers of the FDA. NCTR has recently hired an Associate Director whose primary responsibility will be to identify research needs and opportunities for collaboration with other Centers. However, there is still an urgent need to assess how its activities can be better integrated to address the major needs of FDA. Much of the current research is funded and driven by other agencies.

We also recommend that the Science Board, in collaboration with the relevant BESCs, undertake a review of the ORA to determine synergies and discordances with the respective centers, and to obtain an in-depth analysis of technologies being applied in the field.

The Subcommittee recommends the establishment of a Task Force for Ethnic Minority Health.

Task Force would strengthen the scientific base of the Agency by reducing ethnic health disparities throughout FDA through methods that would include evaluating and understanding the differential effects/responses of patients to drugs, biologics and devices on the basis of ethnic minority status (biologically mediated differences and understanding differences in balance of safety and effectiveness as a function of how products are being used in different communities of

patients and providers). The Task Force would measure and understand the extent to which clinical studies used in the approval process adequately include ethnic minorities, especially when new products will be utilized by ethnic minority patients. (Considerable effort needs to be expended to understand what "adequate" means, given the perils of subgroup analysis and the false positive and false negative problems engendered.) The office will work to ensure that data analyses address drug, food and device effects (both benefits and risks) in ethnic minority populations.

The Task Force would also further assess the need for establishment and the structure of an Office of Ethnic Minority Health and Health Disparities at FDA.

The Subcommittee recommends that the Role of the FDA Science Board be expanded. The Subcommittee strongly believes that the FDA Science Board should continue to report to the Commissioner of FDA. However, its role should be expanded to provide guidance and advice as may be requested by the Deputy Commissioner and the Chief Scientific Officer. The Board must provide active oversight of the science agenda and the actions recommended by the new external boards of advisors.

3.2 Workforce: Securing Critical Scientific Capability and Capacity

The FDA's mission requires it to gather, process and disseminate information. Having a highly skilled workforce that is both capable of fulfilling that function and motivated to do so is essential. Staff have borne the brunt of the increased FDA responsibilities and declining FDA resources. The combination of these two pressures has led to the loss of some of the Agency's best scientists, increasing the burden on the remaining staff. It has created an environment where it is difficult to carry out good but mission-related fundamental research. Staff have an increasing loss of a sense of purpose and vision, borne from an inability to respond to the opportunities challenges of rapidly changing science.

It has become increasingly difficult to recruit both the young and even the more mature scientific talents that should underlie the essence of the Agency. Indeed, the budget and staff of some single faculty labs in academic institutions now exceed that of major FDA centers. For example, CDER has a total of only 54 laboratory-based scientists, 19 laboratory fellows and 11 laboratory-based visiting scientists. CVM has 70 laboratory-based scientists and no laboratory-based fellows or visiting scientists. CBER has 343 laboratory personnel and 77 fellows who spend 50 percent of their time in the lab and 50 percent of their time doing review. They have no visiting scientists. CDRH has 205 laboratory-based personnel, 14 laboratory-based fellows and 10 visiting scientists based in the lab. While it is true that laboratory

research is not the major mission of FDA, the capacity to perform mission-relevant research is absolutely essential if the Agency is to fulfill its mission as discussed in this report and numerous others. After all, three of the six FDA Centers specifically have research in their titles to reflect this need: CDER, CBER and NCTR. A vibrant fellowship and visiting scientists program are essential to provide constant introduction of new ideas and technology. At the same time, FDA must ensure that these programs are structured so that it is a meaningful experience for follows and visiting scientists (i.e., there needs to be a formal mentoring program for these individuals).

As documented by our Subcommittee (Appendices C–K) and the FDA self-assessment process associated with this review (Appendix M), significant gaps exist in most areas of scientific expertise in all Centers and programs, in particular those associated with the newer areas of science. Other than resources needed to fill the gaps, our review, together with external evidence[35], suggests substantial challenges are faced in four other key areas: recruitment, retention, performance and professional development.

The Subcommittee notes that there are a number of "megatrends" that will affect long-term planning, such as an aging workforce, the increasing volume of data, particularly from outside the US, and the increasing volume of work, which is at least partly due to rapidly changing science. These megatrends mean that addressing the problem of science staff capacity and expertise "mix" will require a strong and comprehensive Agency-wide approach, although within this framework, Center specific adaptations and implementation are appropriate. The creation of and ongoing operation of such a program should be driven by the routine assessment of Agency-wide needs for the expertise and scale of science staff requirements. In addition, given FDA's mission, there is a need to develop mechanisms to incorporate the world of expert talent for highly specialized analysis and science while keeping decision making internal to FDA.

[35] See, for example, the 2006 report by PricewaterhouseCoopers, LLP entitled *Improving America's Health IV: A Survey of the Working Relationship Between the Life Sciences Industry and the FDA*, and the IT Infrastructure group's report on the IT workforce.

3.2.1 Finding: The FDA has substantial recruitment and retention challenges.

Recommendation: The FDA should create a distinctive research culture, take concrete steps to hire more high-quality scientific talent, and create better career ladders.

The first step in building a high-quality workforce is recruiting high-quality personnel; the second step is retaining them. The FDA has some advantages in hiring at lower levels because the government offers secure jobs with excellent pension and health benefits. There are two key challenges to recruitment faced at higher levels: a salary cap which makes it difficult to compete with higher paying academic and private sector institutions and a slow and inflexible human resources system. A major challenge to retention is a truncated career path.

Talented and well-qualified individuals are attracted to the FDA by some combination of institutional reputation, excitement about the job in terms of personal creativity and impact, and institutional impact; as well as the prospect of career advancement (i.e., more the chance for job satisfaction with a prospect of future fame and better pay than for current high salaries). That should position the FDA fairly well: if it were strictly about salary, they would have no hope to compete.

As the Subcommittee offers suggestions about the FDA workforce, it is important to recognize that this workforce is mandated to pursue much important public service, but routine, work. They conduct tens of thousands of inspections, review many thousands of applications and pursue hundreds of enforcement actions every year. This transaction work must continue. Thus the challenge is how to have good, solid performers for these important functions while building up a cadre of highly talented researchers, particularly when there is intense market competition from the industrial and academic sectors for the latter.

The Subcommittee recommends that the FDA create a distinctive and exciting regulatory science culture, as described elsewhere in the report. An additional approach would be to establish programs of scientific exchanges between FDA and academia/other scientific organizations. IIRIS is a critical initiative in this regard. The FDA could consider splitting reviewer and combined researcher/reviewer career tracks to facilitate surveillance and statistics methods researchers moving back and forth to academia, the Center for Education on Research and Therapeutics (CERTs), the Reagan-Udall Foundation, sister agencies and even industry. Creating exchange programs with international regulatory agencies, such as the European Agency for the Evaluation of Medicinal Products (EMEA), should also be considered.

The Subcommittee recommends that the FDA develop innovative approaches to recruiting high-quality academic talent. The Subcommittee identified three such possibilities that would work best

together. The first is to institute a substantial fellowship program led by a cadre of full-time peer reviewed permanent regulatory researchers. While FDA has a fellowship program, the numbers are small and it is not clear that it is as competitive as it could be if it were larger and structured to attract the most outstanding individuals. The second is to have a competitive program for tenure-track professionals. The Agency would broadly advertise the tenure-track position. Individuals from the FDA Fellowship program would be eligible, but would have to compete for positions. The third is to aggressively recruit and bring in visiting scholars from academia and regulated industry (perhaps in conjunction with a major medical school or professional society) for one-year positions to work on specific projects in regulatory research (minimizing any concern about conflict of interest). This can be accomplished by expanding the use of Independent Project Analysis (IPA) (secondment with host Agency paying employing organization) Visiting Scholars. This approach has the advantage of providing short-term staff with new ideas and new skills at relatively low marginal cost. An additional advantage with academic IPAs is that they often send their graduate students to work with the Agency. NIH has a longstanding tradition of bringing in highly qualified scientists and academics as IPAs; the Census Bureau and the Bureau of Labor Statistics have worked with the American Statistical Association and the National Science Foundation to create a similar vehicle.

The Subcommittee recommends that the FDA change its existing human resource infrastructure to create better career ladders. First, while the Agency already has more than 100 GS15 technical positions, it should establish more technical GS15 positions to create more career pathways for individuals interested in advancing a scientific rather than a managerial career. (Although Title 42 hiring is more expeditious, it neither provides the employment security, nor the automatic cost-of-living adjustments, that the traditional hiring procedure provides.) Second, the FDA should create the potential for temporary promotions for work on high-priority projects. The Census Bureau provides temporary promotions to staff who are detailed to work on the Decennial Census; FDA could institute the same type of program.

The Subcommittee recommends that the FDA also be provided with human resource flexibility, enabling the Agency to expand the use of Title 42 procedures to ensure hiring flexibility when expeditious hiring is necessary. The FDA should also develop an Agency-wide policy that facilitates "early retirement" and establish a linkage between early retirement and recruitment efforts to acquire new areas of science expertise, e.g., using vacated positions to fill critical gaps. Another approach would permit a routine review of high-priority/high-shortage positions/expertise for purposes of "reclassification" to take advantage of high pay grade, provisions for scarce skills or other special treatments available under government personnel provisions. Finally, the FDA should implement special recruitment programs in high-

priority/high-shortage specialty areas of science. The program should target advanced degree graduates and offer short-term (24–36 months) "interim" positions providing unique regulatory opportunities for career development through participation in unique research or development activities at the Agency.

3.2.2 Finding: The FDA has an inadequate and ineffective program for scientist performance.

Recommendation: The FDA should enhance the program to monitor performance metrics and put the appropriate IT infrastructure in place to track the evolution of those metrics.

The third step to ensuring that the FDA has a high-quality workforce is measuring performance so that good performance can be rewarded and poor performance corrected.

The Subcommittee found that there needs to be more meaningful measures of scientific performance on the part of staff. The lack of metrics has substantial repercussions: it compromises the ability of senior executives to delegate tasks to subordinate managers, it creates a directionless environment in which staff often receive only vague instructions (e.g., "improve safety and efficacy" or "protect and promote public health"), and it leads to the use of poor proxies for the desired results[36]. It is worth elaborating on the last point. If performance is based on a noisy proxy, such as time to review a new product application, the pressure to perform can lead to unintended consequences, such as worse drug safety.

The Subcommittee recommends that systems be put in place to collect data for meaningful retrospective appraisals of performance or prospective analysis of alternative allocations of FDA resources. Several steps are necessary. A scientific basis must be developed to create performance metrics. The appropriate IT infrastructure must be put in place to track performance. Internal resources must be allocated to monitor performance. Finally, internal and external processes (including OMB approval) must be put in place so that decisions based on the metrics can be implemented.

3.2.3 Finding: The FDA has inadequate funding for professional development.

Recommendation: FDA should develop and support a strong ongoing professional development program

[36] As the saying goes among human resource professionals, "If you want outcome 'A' and measure outcome 'B,' don't be surprised if you get 'B'."

to ensure that staff maintains its scientific competence.

The final step is to ensure that staff, once recruited, maintain their scientific competence through refresher classes, access to scientific journals and software, exposure to outstanding seminar speakers, and time allotted to communicate new approaches with each other internally. It is also essential that staff have the time to document the results of their work so that their approach can be verified and validated through scientific review. It is essential that staff attend scientific conferences to ensure that they keep up with new developments in the field.

The Subcommittee found that there appears to be little or no time available for such activities, adversely affecting both recruitment and retention.

The Subcommittee recommends the development of an Agency-wide policy of participation in professional development, including:

- Endorsing attendance of science staff at relevant external professional development conferences and programs, and participation in study groups within professional organizations
- Funding at the Agency level, with Center-level funding to support the cost of participation
- Developing and providing Agency-wide funding (possibly to be shared with the Centers) for external, ongoing technical education and training of science staff in areas identified as high priority in support of the Agency's mission

We estimate that about two months of every staff year should be dedicated to such activities to ensure appropriate levels of professional development. This implies a concomitant staff increase of approximately 18 percent.

3.2.4 Finding: The FDA has not taken sufficient advantage of external and internal collaborations.

Recommendation: The FDA should strengthen its collaboration across Centers and with other government agencies. It should appoint a Director of External Collaborations to administer a competitive external grants program.

The Subcommittee notes that external collaborations are particularly critical for closing the scientific gap by accessing expertise in the emerging sciences and technologies. External collaborations can also help with the implementation of the Critical Path Initiative, as well as with the recommendations of the IOM report, *The Future of Drug*

Safety. The committee acknowledges that as a regulatory Agency, the FDA has clear constraints on the nature and content of relationships with external organizations. Nevertheless, the Subcommittee found substantive examples of creative efforts within the Agency (CBER, CDRH, NCTR and CDER) and is well aware of the value of such approaches at other government agencies. However, the Subcommittee did not find a process for establishing strategic partnerships. Most appear to be a matter of convenience and at the request of other agencies that need work done to support their own missions. FDA needs adequate resources to attract and drive meaningful partnerships with other agencies, academia and industry. The Subcommittee believes that a genuine commitment and sharp focus can help ease near-term challenges and better manage the longer challenges of science staff capacity and expertise within FDA. The IOM Committee recognized the importance of external collaborations to improve FDA's current drug safety system. This was also a common finding of all Subgroups of our Committee.

The Subcommittee found that FDA will not be able effectively to recruit and retain all the scientific expertise it needs in house. In addition, it will be necessary to institute much more extensive and regular involvement of external scientists, with the emergence of new scientific issues. The academic community nationally, together with scientists at sister research agencies, represent an enormous potential resource of relevance to both drug safety and efficacy, and for addressing the issues of human capital.

The Subcommittee recommends that the FDA actively establish ties with extramural scientists with expertise in drug mechanisms and pharmacogenomics to better to integrate such knowledge into pre- and post-market safety assessments, surveillance activities and assessment of product quality. This could include improving collaborative structures for working with other agencies within HHS (CDC, NIH, Agency for Health Care Research Quality [AHRQ], CERTs), as well as other relevant federal agencies (USDA, DHS, VA). The FDA should engage the broader scientific community by developing collaborative programs with NIH Institutes to fund methods research grants relevant to evaluation of research strategies for product evaluation and safety surveillance. The FDA should also organize scientific conferences and/or training programs better to educate outside scientists about FDA practices, procedures and policies. Finally, the FDA should develop principles and guidance on how to interact through public-private partnerships on safety surveillance to support sound Agency judgments on safety signals and alerts.

The Subcommittee recommends that the FDA institute more opportunities for cross-Center interaction to establish best practices. Such interactions should be used to ensure appropriate consistency of approach, more formal collaborative structures for work with other agencies (e.g., with CDC, Food Safety and Inspection Service (FSIS)/USDA, and the Environmental Protection Agency for food

safety, CDC for vaccine safety; CMS and VA for drug safety), as well as increased attention to surveillance systems for food safety for humans and animals. Studies of drug mechanism need to be integrated with the collection of data from clinical trials and surveillance programs to facilitate rapid and accurate assessments of potential safety concerns. As discussed above, increased opportunities for in-depth scientific interactions with academic researchers and other outside scientists are needed.

The Subcommittee recommends the establishment of a robust program to foster external collaborations including: appointing a Director of External Scientific Collaborations with appropriate funding to establish meaningful external programs based on rigorous peer review; including a competitive grants program (possibly through the Reagan-Udall Foundation) for joint projects with academic institutions and industry judged to have major impacts upon regulatory science; expanding use of Cooperative Research and Development Agreements (CRADAs); and initiating more joint scientific programs with sister agencies.

The Subcommittee recommends that FDA develop the capability to rapidly mobilize an expert task force to deal with potential emerging acute problems. Such a task force might involve external scientists — a sort of *National Guard* for product safety issues. One might envision a training program like the Epidemic Intelligence Service (EIS) at the CDC. In addition to a rapid response capability, the FDA would be creating an ever expanding cohort with critical expertise in regulatory science that could dramatically improve regulatory science across the globe. One just need look at the impact of the EIS program. Established in 1951, the EIS program has trained thousands of epidemiologists who have provided critical public health leadership. Furthermore, the EIS program has had a global impact as other countries have, with the CDC's assistance in many cases, established similar programs. Given unique considerations between the public and private sectors in the area of regulatory science, conflicts of interest for external scientists would be carefully vetted and managed.

3.3 Information Infrastructure

All of the working group subcommittees discovered significant deficiencies in the ability of regulatory programs to access and utilize information (see Section 7 within Appendix K, Information Technology, for a glossary of IT terminology). The discussion on the state of the information processing capability and information technology at the FDA has been structured as follows:

1. Science and regulatory program considerations, including quality; safety and efficacy; new science; and food safety

2. Specific technology infrastructure and practice considerations, including technology infrastructure, best practices, workforce and legislative activity

The Committee finds that an information crisis is putting the FDA's mission at risk. The FDA is dependent on accurate and timely information to deliver its regulatory mission. It is critical that the discussion on "information technology" be first and foremost a discussion on information and then a discussion on technology.

3.3.1 Finding: The Subcommittee believes that there is evidence of important, but slow, progress to improve information sciences and technology at the FDA over the past few years, yet significant gaps remain.

Recommendation: Based on the evidence of important foundational work to date in IT and yet the continued existence of critical IT capability gaps, there should be significant investment in IT at the FDA to accelerate progress toward an information processing and communications capability that can support all regulatory science.

The Subcommittee found the following evidence that supports the existence of excellent and important work to date in the IT arena at the FDA:

- New Chief Information Officer (CIO), Chief Operations Officer (COO) and Chief Technology Officer (CTO) have strong track records at other government agencies.
- Internal IT governance boards are now operational with strong program/scientific support and participation.
- IT activities are evolving toward an enterprise model of management.
- Standards activities are in process with strong external collaboration and FDA is providing important leadership among standards-setting bodies.
- Strong collaborations with external partners in other areas, including data modeling, are also taking place.
- Recognition of key challenges is consistent across large groups of internal FDA stakeholders, suggesting that it will be possible to accomplish change.
- Business process delineation is in early stages, but is progressing well.

- The Office of the CIO, under the leadership of a new CIO, is championing five critical initiatives to accelerate progress of critical capabilities and best practices.

The Subcommittee found critical capability gaps in the area of information technology and science, enumerated in detail below and in the IT findings in appendix K, that compromise the FDA's ability to fulfill its regulatory mandate.

The Subcommittee recommends that investment be made in IT to further support and accelerate these activities. Specifically, it believes that the FDA will be able to deploy the new investment to successfully drive toward a more robust information and technology environment capable of supporting regulatory science.

3.3.2 Finding: The FDA lacks the information science capability and information infrastructure to fulfill its regulatory mandate.

Recommendation: FDA IT must develop the intramural capability to support all regulatory science activities and should catalyze the development of multi-sectoral shared health information exchanges to support industry innovation and fulfillment of regulatory responsibilities.

The Subcommittee found that the FDA's current critical information supply chains are, at best, inefficient, cost intensive and prone to promote errors in regulatory science due to the inability to access, integrate and analyze data. Incredibly, critical data resides in large warehouses sequestered in piles and piles of paper documents. There are no effective mechanisms to protect these paper records, which include very valuable clinical trial data. 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 cannot credibly process, manage, protect, access, analyze and leverage the vast amounts of data that it encounters. Consequently, the FDA's ability to support industry innovation and regulatory activities is compromised.

The Subcommittee recommends that the FDA define and develop clear business processes to support regulatory science and mission. Leveraging these business processes, the FDA should launch the necessary intramural and extramural activities to develop efficient standards-based health exchange capability. The FDA should aggressively pursue access to health and public health databases for adverse-event identification and surveillance for risk identification. Similarly, by leveraging standards and access to growing health

information exchanges, the FDA should catalyze and participate in the development of efficient pre-market and post-market data exchange networks required to ensure the quality, safety and efficacy of medical and consumer products as defined by its regulatory mandate.

The Subcommittee recommends that the FDA should work closely with other government agencies domestically and internationally in areas where there is mission overlap or interdependence, e.g., food safety, border control for imported products, etc., where DHS, CDC and other departments or agencies may be involved. These collaborations are critical to ensure that gaps in regulatory coverage do not occur due to poor communication, poor understanding of integrated business processes or a lack of interoperability.

The Subcommittee found that the FDA lacks the capability to leverage technology to assist in the inspection and monitoring of manufacturing sites, transportation vehicles and product. For example, it would be very useful if the FDA were able to position sensing devices onsite at manufacturing plants, in transportation vehicles or in the packaging of products that could detect purity and/or contamination. Ideally, these data and information would be transmitted back through the appropriate information supply chains in real time and inform the inspecting authorities of risks. Until the FDA can develop the requirements for these capabilities and work with the private sector so that these capabilities emerge, the manufacture and transportation of its regulated products will not be adequately monitored. The extraordinary number of sites that must be monitored and the dearth of inspectors translate into the FDA's inability to fulfill its quality assurance mandate.

The Subcommittee recommends that the FDA provide requirements and funding to stimulate the development and deployment of these critical remote sensing technologies. Attention should be paid to all manufacturing sites, food supply chain and transportation infrastructure regulated by the FDA, such as rail cars.

The Subcommittee recommends that the FDA develop the capacity to do advanced data mining and use analytical methodologies and tool development for large databases, as well as the development of new statistical methods and trial designs. This includes adverse event and signal detection, rapid portable diagnostic/analytic testing, the development of risk-based models for selection of manufacturing inspections, risk communications science and enhanced reviewer tools such as data standards, electronic submissions, data mining and analysis, electronic product listing and tracking.

The Subcommittee found the lack of legislative and policy action is resulting in slow adoption of critical technology, data and information standards and practices throughout the medical product, food and cosmetic industries, which prevents the FDA from having timely access to the data required to execute its regulatory mission.

The Subcommittee recommends that the FDA needs to work closely with the legislative branch to develop the mandates to drive adoption of data sharing 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.

3.3.3 Finding: The FDA cannot provide the information infrastructure support to regulate products based on new science.

Recommendation: The FDA must develop the capability to innovate in information science and technology to better support its regulatory mandate and more specifically to support regulatory activities for new science.

The Subcommittee found that the FDA information technology resources, workforce and infrastructure prevent it from delivering critical innovation in IT that is required to support its current and expanding regulatory mandate.

The Subcommittee found that the FDA lacks the information sciences and infrastructure to support new science. As previously noted in this report, the FDA is continuously facing the challenge of regulating products based on rapidly evolving science and technology. The FDA lacks the capability to manage the complex data and information challenges associated with rapid innovation, such as new data types, data models and analytic methods.

The Subcommittee recommends that the FDA dedicate IT staff to IIRIS (described previously in this report) to ensure that the Agency will anticipate evolving information science needs based on new science. Furthermore, the IIRIS information activity should establish extensive external collaborations with other government agencies, academia and industry. Safety as well as innovation will be at risk if information science cannot support critical surveillance and investigation activities.

3.3.4 Finding: The FDA IT infrastructure is obsolete, unstable, and lacks sufficient controls to ensure continuity of operations or to provide effective disaster recovery services.

Recommendation: The FDA should identify and implement high-return enhancements of FDA IT infrastructure.

The Subcommittee found that FDA data and information infrastructure is at risk due to an evolving but incomplete migration to a robust enterprise model. As many as 80 percent of the network servers are more than five years old and have exceeded their recommended service life. In addition, critical network components remain scattered around the agency rather than being centralized in data centers that would provide the necessary security, redundancy and continuity of operations assurances. Thus the network and telecommunications infrastructure is not only inadequately protected, but many of its critical components have exceeded their recommended life expectancy. Not surprisingly, it has been reported that during a 2007 *E. coli* outbreak due to contaminated spinach the FDA's response was hampered by outages in its email systems. Outages are occurring in other systems as well.

The Subcommittee found that in addition to deficiencies in its technology and communications platform, the FDA lacks many basic tools to support science and regulatory services. Specifically, the agency lacks the ability to adequately store data from clinical trials or adverse-event reporting. The vast majority of these data are still paper based and sit in large warehouses where it is not possible to efficiently access the data. The agency lacks adequate tools to search data, model the data and analyze the data. FDA staff repeatedly emphasized the incredible missed opportunities that exist due to the inability to conduct safety and efficacy studies as a consequence of these deficiencies in storage, search and core scientific tools.

The Subcommittee found that the laboratory community at the FDA lacks the necessary computing infrastructure due to its need for specialized tools. The FDA must address the need of the laboratory community to have a segregated network that would provide the laboratories with their required scientific infrastructure, while at the same time providing the appropriate level of network security.

The Subcommittee found that the FDA's media development and broadcasting capability is inadequate. The FDA's overall mission is dependent upon its ability to effectively communicate with industry and consumers in a timely and robust manner. In addition, there are many emerging communication platforms, e.g., Web 2.0 capabilities, and strategies that the FDA has yet to establish as an accessible capability to offer its programs.

The Subcommittee recommends that the FDA accelerate its 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. The FDA must 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 the general FDA network infrastructure. The FDA must also 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 tools to enable the FDA to access and analyze these and other scientific data. Finally, the FDA must establish state-of-the-art communications strategies, platforms and training programs to ensure that the FDA effectively communicates with industry, stakeholders and consumers.

The Subcommittee found that the FDA does not follow IT best practices. It has not currently implemented and/or appropriately staffed to provide effective governance, capital planning/investment control and enterprise architecture activities. The consequences of this are manifested in the deficiencies noted above: an unreliable technology infrastructure, inability to support science and inability to obtain required data in a timely manner to conduct its regulatory mission at acceptable levels.

The Subcommittee recommends that the FDA evaluate critical IT best management practices. Based on a comprehensive evaluation, the FDA IT leadership should work with its scientific leadership to establish effective IT governance. Furthermore, working closely with HHS Chief Enterprise Architect, the FDA should ensure that it has effective capital planning/investment control and enterprise architecture activities in place.

3.3.5 Finding: The IT workforce is insufficient and suboptimally organized.

Recommendation: Strengthen and organize the IT workforce to ensure that it can support the rapid evolution of the FDA information science and technology infrastructure.

The Subcommittee found that the workforce deficiency is present at all levels of the IT organization. As noted above, the critical best practice areas of governance, enterprise architecture and capital planning and investment control do not have sufficient resources, and they have not been able to deliver the required visioning and oversight over operations.

The Subcommittee found that the deployment and management of IT staff are highly decentralized, which results in a poorly coordinated effort with poor quality control. It is clear that the information infrastructure is seriously compromised and inadequate. At least part of the reason is the turnover at the top level of the organization: in the past five years, the FDA has had four CIOs.

The industry benchmark for appropriate IT staffing [IT staff:total staff] is 5.8 at the FDA. While this is consistent with most industry standards, the FDA represents a very different type of organization in that it has to deal with complex scientific issues and rapidly emerging areas that require a higher ratio. Furthermore, since the FDA does not operate within an enterprise model, these staff members are not optimally contributing to the FDA technology needs, so the number of IT staff it needs is going to be greater than the industry benchmark and therefore, the FDA is functionally understaffed.

Finally, the Subcommittee found that the FDA has inadequate processes for the recruitment and retention of IT staff. It also does not have a performance measurement program and does not invest sufficiently in professional development.

The Subcommittee recommends increasing the IT staff to total staff ratio to address resource constraints and providing full support to the CIO in centralizing the infrastructure. It also recommends that the FDA develops a performance measurement program by defining required skill sets for the FDA's information technology workforce. The subcommittee recommends that the FDA develop strategies for recruitment and retention of critical informatics staff, especially in the areas of new science, particularly focusing on developing career ladders that will compete with the private sector, such as instituting promotions based on technical expertise.

Finally, the Subcommittee recommends that the FDA develop and implement strategies for professional development that will facilitate the agency's need to operate at the forefront of regulatory science. In recognition of the important role of contractors, it should implement training procedures to enable IT staff to monitor and evaluate contractor performance. An important component of the training program should be an informatics fellowship program that may leverage IPA agreements.

Section 4 Overarching Findings of this FDA Review

4.1.1 Finding: The FDA has experienced decreasing resources in the face of increasing responsibilities.

Recommendation: The FDA resource gap must be corrected to enable the Agency to fulfill its regulatory mandate.

The Subcommittee was not in a position to conduct a zero-based budget analysis for FDA, nor was it asked to do so. However, the Subcommittee was able to review publicly available information and directly observe the overall stress within the Agency while conducting this review. The Subcommittee finds that, without a significant increase in resources, its recommendations will be superfluous. Therefore, the Subcommittee feels compelled to comment upon resource issues and recommendations by others.

Food Safety

In his recent Executive Order announcing an Inter-Agency Working Group on Import Safety, President Bush stated that the current system must be fixed "within available resources[37]." We can state unequivocally that the system cannot be fixed "within available resources." For example, the Coalition for a Stronger FDA estimates that an excess of $130 million is needed to devise and implement a new food import system[38]. This is in addition to the funds needed to modernize the safety standards for fresh produce and other raw foods, and to develop and implement inspection programs to audit industry compliance, which are estimated to be $50 million for CFSAN and $160 million for the ORA. Infrastructure improvements to enhance existing laboratories, equipment and personnel would require an additional $10 million for CFSAN and $40 million for ORA. These estimates do not include funds required to modernize assessment of animal derived products (including milk and eggs) by CVM.

IT and Product Safety

The remediation of the IT deficiencies currently present at the FDA require a very significant increase in funding that is justified based on two factors: the evidence of good, but slow, progress at the FDA in the IT arena, and the fact that all FDA programs depend on a strong

[37] See White House Executive Order: Establishing An Interagency Working Group on Import Safety, http://www.whitehouse.gov/news/releases/2007/07/20070718-4.html

[38] Coalition for a Stronger FDA website, http://www.fdacoalition.org/

information backbone. Based on publicly available information, the overall IT budget for the FDA is $200 million — compared to $500 million for the CDC. While the FDA has a total of 12,000 staff and the CDC has a total of 14,000 staff, in many ways the IT operational activities of the two agencies are similar. Specifically, each Agency must manage complex scientific data, set data sharing standards, support internal scientific operations, and support extramural capability to reduce risk to the public. However, the CDC average IT expenditure per staff person is approximately $35,000, compared to $16,000 at the FDA. Not only must the FDA deliver capability in the terrorism preparedness and response arena that is very similar to that at the CDC, but the FDA must also regulate approximately $1 trillion worth of consumer goods. It seems to follow that its IT budget should easily surpass that of its sister Agency, the CDC; however, the FDA IT budget is only about 40 percent of the CDC IT budget. In addition, although the IT-staff-to-total-staff ratio of 5.8/100 is close to industry benchmark of approximately 5/100, it is important to recognize that these benchmarks do not take into account the complexity of the FDA scientific mission or the need for the FDA to support the development of national and international information sharing capability.

The FDA must invest in the development of large-scale, sustainable data sharing infrastructures to 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. As benchmarks, we can examine other government investments. Examples of major CDC IT investments (estimated costs for 2006-2008 from http://www.cdc.gov/od/ocio/CDC_IT_Strategic_Plan_FY_08-12.pdf) include the following: BioSense ($164 million), National Electronic Disease Surveillance Systems (NEDDS) ($75 million)>$), and the National Select Agent Registry ($20 million). The cost estimates for these CDC systems do not include the tens of millions of dollars already invested in them over the previous 3−5 years. DHS is investing in the National Biosurveillance Integration System (NBIS) ($15 million for first year of development), and the National Cancer Institute is investing in the Cancer Biomedical Informatics Grid (CaBIG) ($20 million/year for first three years).

The FDA must also have a sizable budget to support extramural activities so it can 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 collaboratively 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.

The IOM 2006 report, *The Future of Drug Safety*, estimates that an investment of as much as $350 million will be necessary so FDA staff can access the necessary data bases, establish critical external collaborations and perform selected studies[39]. We are aware that surveillance and access to databases and other areas related to drug safety are included in the Food and Drug Administration Amendment Act of 2007 (the user-fee reauthorization act). However, the legislation provides only a small portion of the needed increase. A decade ago, it was estimated that $100 million would be required to strengthen the FDA's post-market review system — this was an old estimate and much less robust than the system recommended by the IOM report, *Future of Drug Safety*[40].

Emerging Science

The establishment of public/private partnerships for addressing the Critical Path Initiative and areas of emerging science related to drug safety, through the Reagan-Udall Foundation, is authorized at a level of only up to $1.25 million in federal funds, respectively. The IOM report, *Challenges for the FDA: The Future of Drug Safety*, which focused on addressing the FDA's resources, indicated that funding a single "new science program" could require $15 million. Few argue over the value of FBI's investment in genomics to establish the felon database. And few argue over the establishment of an investment in a genomics institute at NIH. Both agencies recognized the value proposition of these investments and were able to invest NEW money — FDA needs the same NEW investment. As pointed out in the IOM *Challenges for the FDA* report, $15 million total is currently available in CDER for all research conducted by the Center[41]. Therefore, it is clear that the increases have to be substantial.

FDA must be able to put an IT infrastructure in place so that it can regulate these fast-developing "new science" fields, such as panomics, wireless health care devices, medical imaging and nanotechnology. A number of investments for each field are necessary to cover the cost of the development of a team, analysis of the emerging risk, and development of an information technology capability to support the regulatory role of the FDA for the new science area.

In sum, the current resources have clearly been insufficient to support the regulatory science and regulatory services of the FDA. The Subcommittee notes that the Coalition for a Stronger FDA advocates a total of $175 million in increased appropriations for the Agency for 2008 (over the fiscal year 2007 budget and over increases provided by the Food and Drug Administration Amendment Act of 2007) with

[39] IOM (Institute of Medicine) 2007. The Future of Drug Safety: Promoting and Protecting the Health of the Public. Washington, DC: The National Academies Press.
[40] IOM (Institute of Medicine) 2007. The Future of Drug Safety: Promoting and Protecting the Health of the Public. Washington, DC: The National Academies Press.
[41] IOM (Institute of Medicine) 2007. Challenges for the FDA: The Future of Drug Safety. Washington, DC: The National Academies Press.

additional increases thereafter so that by 2013 the total appropriated budget would be $2.8 billion. However, in light of recent events regarding food safety, the Coalition has begun advocating for a $310 million increase, with $250 going toward food safety. The gaps identified by our Subcommittee suggest that even this proposed amount may not be sufficient to begin to address the most critical scientific deficiencies at the FDA. Therefore, the Subcommittee urges the FDA with the Science Board to develop a business plan for science in the process of establishing the strategic plan outlined in this report. The Subcommittee notes that in addition to preventing public health crises, the recommendations outlined in this report will significantly improve the effectiveness and efficiency of developing breakthrough drugs and devices.

4.1.2 Finding: Recommendations of excellent FDA reviews are seldom followed.

Recommendation: The Office of the Commissioner should develop and report to the Science Board a comprehensive plan for timely and effective implementation of these recommendations.

There is a long history of excellent reviews of the FDA that have been followed by little to no action taken to achieve the recommendations. Our final recommendation is based in our belief that effective resolution of the issues outlined in this report is urgent. In contrast to previous reports that have issued many of the same warnings, there are now sufficient data proving that failure to act in the past has jeopardized the public's health. We, therefore, urge the FDA to develop a comprehensive plan that includes how and when the Agency will respond to these recommendations, and to report that plan to the Science Board. We also recommend that this plan be aligned with the 2009 budget process in order to align the resources with the proposed response.