

Advancing Regulatory Science for Public Health



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Department of Health and Human Services; U.S. Food and Drug Administration
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Advancing Regulatory Science for Public Health

2 EXECUTIVE SUMMARY

3 THE PROMISE OF REGULATORY SCIENCE

4 I. Accelerating Delivery of New Treatments to Patients

6 II. Improving Pediatric and Child Health

8 III. Protecting Against Emerging Infectious Diseases and Terrorism

11 IV. Enhancing Safety and Health Through Informatics

13 V. Protecting the Food Supply

14 VI. Modernizing Safety Testing

16 VII. Meeting the Challenges for Regulating Tobacco

17 A COLLABORATIVE IMPLEMENTATION FRAMEWORK

EXECUTIVE SUMMARY

OVERVIEW

Recent breakthroughs in science and technology — ranging from sequencing of the human genome to advances in the application of nanotechnology to new medical products — have the potential to transform our ability to prevent, diagnose and treat disease. These developments will result in moving treatment strategies towards approaches that are tailored or personalized to individual patients, thus maximizing the benefit of treatments while decreasing their safety risks. Similarly, advances in research and information technologies are enabling us to more efficiently identify microbial pathogens, track food contamination outbreaks and determine where foods and other FDA-regulated products are produced or manufactured, how they are transported, where they go and who uses them. These tools also can play an important role in preventive health by enabling more comprehensive immunization strategies, especially in the face of emerging pandemics.

For these advances to reach their full potential, the Food and Drug Administration (FDA) must play an increasingly integral role as an agency not just dedicated to ensuring safe and effective products, but also to promote public health and participate more actively in the scientific research enterprise directed towards new treatments and interventions. We must also modernize our evaluation and approval processes to ensure that innovative products reach the patients who need them, when they need them. These new scientific tools, technologies, and approaches form the bridge to critical 21st century advances in public health. They form what we call *regulatory science: the science of developing new tools, standards and approaches to assess the safety, efficacy, quality and performance of FDA-regulated products.*

This document outlines a broad vision for advancing regulatory science and unleashing its potential to improve public health. It discusses the role of the FDA, working with partners, to strengthen the field, both within the agency and throughout the Nation.

The document is organized into two sections: (1) The Promise of Regulatory Science and (2) A Collaborative Implementation Framework. The first section provides background on the emerging and promising field of regulatory science as well as examples of current activities. It then goes on to explore seven different public health areas in which advancements in the field can help deliver better, safer, more innovative products to Americans. The second section lays out a strategic framework that will guide FDA as we lead this nationwide effort to advance regulatory science and leverage its potential to fulfill the agency's fundamental mission — to promote and protect the public health.

THE INITIATIVE

FDA proposes to build on the success of the Critical Path Initiative and other projects by leading an effort to advance regulatory science through its new Regulatory Science Initiative. This initiative will be supported by a four-part framework, outlined in greater detail in the final section of this document.

- *Leadership, coordination, strategic planning and transparency to support science and innovation*
- *Support for mission-critical applied research, both at FDA and collaboratively*
- *Support for scientific excellence, professional development and a learning organization*
- *Recruitment and retention of outstanding scientists*

With the President's \$25 million budget request for fiscal year (FY) 2011, FDA plans to expand ongoing efforts within the agency and build additional partnerships with academia, industry and government around the country. A new office dedicated to regulatory science will lead strategic devel-

opment and coordination within FDA, and early efforts will focus on recruiting key personnel and building senior leadership.

In FY2011, the bulk of the budget will be used to mobilize external collaborations and partnerships and support studies in four major regulatory science research areas:

1. Transforming Product Development for Patients: Bringing Progress to Patients
(eg: Methods for Modernizing Toxicology, Biomarkers for Personalized Medicine, the Stem Cell Initiative and Updating Drug Review Standards)
2. Science to Address Emerging Technologies in FDA-regulated Products
(eg: Nanotechnology and Expertise to Regulate New Animal Biotech Products)
3. Information Sciences for Health Outcomes
(eg: Medical Device Registry and Scientific Computing for Data Analyses)
4. Addressing Unmet Public Health Needs
(eg: Nutrition and Public Health)

Activities in FY2011 will also set the stage for a network of Centers of Excellence in Regulatory Science to be integrated with expanded intramural FDA research and with other clinical research networks. Funding for external programs would be competitive and focus on pilot and feasibility studies to form Centers of Excellence.

This document discusses in detail how advances in regulatory science can speed progress in FDA's high-priority public health areas.

There is no single discovery — no magic bullet — to address our unique set of modern scientific regulatory challenges. But one thing is clear: if we are to solve the most pressing public health problems we face today, we need new approaches, new collaborations and new ways to take advantage of 21st century technologies. And we need them now.

THE PROMISE OF REGULATORY SCIENCE

What is regulatory science?

Regulatory science is the science of developing new tools, standards and approaches to assess the safety, efficacy, quality and performance of FDA-regulated products.

What is the potential of regulatory science?

The field of regulatory science — both the knowledge generated in developing new tools and the tools themselves — has the potential to inform a broad range of health-related advances, involving numerous diseases and conditions. For example, a project to explore how to characterize and predict undesired immune responses that can alter or block the effects of recombinant proteins and monoclonal antibodies can demonstrate relevance to the treatment of cancer, rheumatoid arthritis and other diseases. The knowledge generated from such studies may well be applicable across entire classes of food and medical products and could help better ensure that such medicines are both safe and effective.

Regulatory science does not take place only in laboratories. It involves scientific tools and information-gathering and analytical systems to study data, people, health systems and communities. To be most effective, advances in regulatory science must be fully integrated into the entire product

development process. Outreach and collaborative efforts are integral to predicting the failure or success of new discoveries and technologies early in development, reducing product development costs. Advances in regulatory science will help make the evaluation and approval process more efficient, helping to deliver safe new products to patients faster and strengthening the ability to monitor product use and improve performance, thus enhancing patient outcomes.

What are the priorities for regulatory science?

With a focused agenda and targeted investment of human and financial resources, FDA will continue its work with its partners to transform the culture and science of product research, development, and evaluation — and infuse the process with new creativity.

The pages that follow will illustrate the current activities and future opportunities for regulatory science to tackle some of the most important and pressing public health challenges facing Americans today:

- I. Accelerating Delivery of New Medical Treatments to Patients ... (page 4)
- II. Improving Pediatric and Child Health ... (page 6)
- III. Protecting Against Emerging Infectious Diseases and Terrorism ... (page 8)
- IV. Enhancing Safety and Health Through Informatics ... (page 11)
- V. Protecting the Food Supply ... (page 13)
- VI. Modernizing Safety Testing ... (page 14)
- VII. Meeting the Challenges for Regulating Tobacco ... (page 16)

I. ACCELERATING THE DELIVERY OF NEW MEDICAL TREATMENTS TO PATIENTS

Recent U.S. investments in biomedical research have dramatically expanded our understanding of biology and disease. Still, the development of new therapies is in decline, and the cost of bringing them to market has soared. In short, we must take advantage of every opportunity to improve the effectiveness and outcomes of healthcare and address growing threats to the strength and innovation of the U.S. biotechnology industry in order to ensure that the best medical treatments are made available to patients in a timely fashion.

What has FDA done?

As a result of the successes of the Critical Path Initiative and other projects, FDA scientists have been instrumental in a number of regulatory science achievements aimed at increasing the practical value of basic discoveries. This is done to ensure that patients have access to the most cutting-edge medical treatment possible. By leveraging existing resources and harnessing the vast knowledge of scientists in its Centers, FDA has established itself as an integral part of the healthcare paradigm. Some of the aforementioned achievements include:

- *Methods for stem cell characterization*

In collaboration with other scientists, FDA scientists developed a method and identified gene biomarkers for “stemness” — that is, for the extent of differentiation in several lines of stem cells. The scientists developed tests and standards to establish the presence of different types of stem cells. These methods can now be used to ensure that undifferentiated stem cells, which may increase the risk of stem cell treatments, do not contaminate final, more differentiated stem cell products that are administered to patients. (Bhattacharya, et al, Blood 2004. 103:2956-2964.)

- *Personalized treatment for cancer*

The “I-SPY 2 TRIAL,” launched in March 2010, represents a groundbreaking new clinical trial model

that will help scientists quickly and efficiently test the most promising drugs in development for women with higher risk, rapidly growing breast cancers. During the trial, drugs in development are individually targeted to the biology of each woman's tumor using specific genetic or biological markers, known as "biomarkers." By applying an innovative trial design, researchers will use data from one set of patients' treatments to treat other patients – more quickly eliminating ineffective treatments and drugs. The I-SPY 2 trial was developed under the Biomarkers Consortium, a unique public-private partnership that includes the FDA, the National Institutes of Health, and major pharmaceutical companies, led by the Foundation for the National Institutes of Health.

What can FDA do with increased investment in regulatory science?

Although developments in science and technology hold great potential, the ways in which new therapies are developed and tested remain underdeveloped and underappreciated. As FDA's independent Science Board found: "American lives are at risk" because ...

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.¹

Without advances in regulatory science, promising medical therapies may be discarded during the developmental process simply because we lack the tools to recognize their potential, or outdated evaluation methods may unnecessarily delay their approval. Conversely, countless dollars and years may be wasted assessing a novel therapy that is later shown to be unsafe or ineffective.

With creative advances in regulatory science, we can change the landscape entirely. We can modernize product development and develop new tools, standards, assays, disease models and science-based pathways to improve the speed, efficiency, predictability, capacity and quality of the entire process, from development to evaluation to manufacturing. Here are some areas in which FDA can make a lasting impact:

- *Safer pain medications*

We are facing a global epidemic of prescription pain medicine abuse and misuse. At the same time, patients in agonizing pain are often left undertreated. New pain pathways have been discovered and new medicines are being developed that can help. But to accelerate the delivery of new treatments to patients, we need to find better pain models, measurement tools (including patient-reported assessments) and clinical trial designs to enable development of effective medications with less potential for abuse.

- *Vaccines, drugs and diagnostics for tuberculosis*

FDA is supporting exciting research into treatments to prevent, diagnose and treat drug resistant tuberculosis (TB) and to develop TB vaccines, needed to protect millions of people everywhere, including U.S. citizens, travelers and troops. We must develop approaches that can more quickly evaluate TB treatments and vaccines, including identifying markers that can predict cure and protection. We must also develop tests that can more rapidly and accurately diagnose TB, including those that determine when TB is resistant to certain treatments.

¹FDA Science Board, FDA Science and Mission at Risk, Report of the Subcommittee on Science and Technology, November 2007. http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4329b_02_01_FDA%20Report%20on%20Science%20and%20Technology.pdf

- *Greater availability of generic drugs*

Generic drugs make up more than 70 percent of the prescriptions filled in this country and, for many, are the only solution to affordable treatment. Still, many products do not have generic alternatives even though patents for the reference products have expired. More generic products could be made available if the difficulty in determining bioequivalence for some products could be overcome, but metered-dose inhalers, dry-powder inhalers, certain topical products and products that are not systemically absorbed present challenges in determining bioequivalence. We must enhance our research into developing validated methods for determining bioequivalence for these products so that quality, lower-cost generic products can become more widely available.

- *Modernized manufacturing and product quality*

FDA is leading efforts on “Quality by Design (QbD),” which applies regulatory science to modernize the understanding and control of medical product manufacturing processes. Advances in regulatory science will not only ensure better quality, but could also lower development and manufacturing costs. Areas of investigation supported by FDA include (1) continuous processing, in which materials constantly flow in and out of the equipment and reduce overall manufacturing time and cost; (2) the use of process analytical technology (PAT) to monitor and control manufacturing processes as opposed to just testing products; and (3) new statistical approaches to detect changes in process or product quality. Applying these approaches will help control complex manufacturing processes, enhance their efficiency and provide more reliable products to patients. In addition, new technologies such as flexible manufacturing facilities and the use of modular and disposable equipment can speed production of products in routine and emergency situations.

There is much at stake for public health. FDA will continue to strengthen mission-critical science within the agency while exploring new and exciting partnerships with other government entities, industry, and academia with the intent of transforming lives and safeguarding the public’s health.

II. IMPROVING PEDIATRIC AND CHILD HEALTH

Children are not just small adults. They have unique health and developmental characteristics that affect how they respond to food and medical products. Regulatory science at FDA holds great promise for bridging the gap in our scientific knowledge about how medical treatments affect children and developing new therapies on their behalf. Although developmental biology and studies of children are active areas of biomedical research, findings are often not translated into product development or clinical studies that assess children as a distinct and separate subpopulation. To provide children with proper nutrition and safe and effective medications, we must understand the effects of growth and how children differ from adults in metabolism, behaviors and hormonal influences.

What has FDA done?

FDA has been committed to addressing the special considerations needed for assessing medical products for children and young adults. These include science to address how development, age and growth may affect how treatments work and effect health outcomes in children. FDA has focused attention on the science required for addressing how drugs behave in children and worked to design studies to address these concerns. Through a combination of legislation, particularly the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA), and scientific work both within and outside of FDA, many studies have been conducted to assess how drugs behave in children versus adults. These studies have resulted in labeling changes for over 350 marketed medical products, including those noting differences in unique pharmacokinetics, dosing adjustments, and enhanced safety information for children. One such study is noted below.

- *Addressing adolescent suicide resulting from antidepressant use*

For years, some patients being treated for depression with antidepressants reported having suicidal thoughts and in many cases attempted suicide. This led to the belief that antidepressants may have an “activating effect” that allows patients to follow through on their suicidal impulses. Several studies conducted in the 1990s concluded that there was, in fact, no link between antidepressants and the risk of completed suicide. However, in 2003, data from several pediatric trials were analyzed and suggested that antidepressants may have led to attempted suicide and increased suicidal tendencies in children. After an FDA-convened advisory committee meeting in 2004, the FDA embarked on its own investigation of the data collected by eight industry sponsors of 12 marketed antidepressant products. Data were compiled from 372 clinical trials with 99,231 participants, much of which was unpublished sponsor data that had not been utilized in previous studies.

The results of this extensive effort of multi-study comparisons by the FDA resulted in several important findings and conclusions. First, there was no evidence of increased suicide risk in the adult population taking anti-depressants. However, when the studies were analyzed by age, an increased risk of suicide was found in adults under 25 years old. This study prompted an understanding that suicidal thoughts and completions tied to antidepressants are age-dependent with increased risk in people under 25, no effect in ages 25-65 and a potentially favorable effect on reducing suicide in adults over age 65. This resulted in FDA placing warnings on the labeling and medication guides. Without the ability to combine data from multiple clinical studies and to use analytical tools and advanced statistics to assess these data, this important finding would not have been made.

What can FDA do with increased investment in regulatory science?

Regulatory science provides the opportunity to examine the unique biology of children, apply that understanding to the science of product development and evaluation — and keep our kids safe and healthy. Here are some ways in which we can safeguard the next generation:

- *Ensuring the safety of medical products*

FDA has already begun this work through projects such as the Safety of Key Inhaled and Intravenous Drugs in Pediatrics Initiative, which is examining the effects of sedatives and anesthetics on children and infants. The project will have a significant effect on pediatric and child health — more projects like this are urgently needed.

- *Securing our food supply*

Children are particularly vulnerable to food-borne pathogens. They are more likely to get sick, even die, from food-borne illness than the general population. A major focus of FDA’s interest in regulatory science is the development of more rapid and practical methods for detecting microbial pathogens in food and equipping FDA’s labs to test multiple food samples for contaminants at once. In addition, FDA must enhance the scientific understanding of the causes of food-borne illness so that feasible interventions can be designed and implemented to effectively reduce risk.

- *Preventing tobacco use in children and youth*

We know that efforts to prevent tobacco use are particularly effective when targeted at children and youth. With new authorities granted under the Family Smoking Prevention and Tobacco Control Act, FDA can propose and implement restrictions on advertising and marketing targeted to children and youth to reduce initiation of tobacco use. FDA needs to enhance its understanding of which industry activities have the greatest effect on youth smoking to promote regulatory efforts to block them. Measuring the effects of these actions on initiation will make sure that FDA is able to meet its goals.

- *Combating obesity*

More than 17 percent of children and youth under age 20 are obese, putting them at risk for cardiovascular disease, type 2 diabetes and other chronic diseases. This makes clear the critical importance of FDA's authority over food labeling, an essential means for informing consumers about the nutrition content of their foods. Health reform legislation signed into law by President Obama extends nutrition labeling requirements to chain restaurants and vending machines. To most effectively exercise this authority, FDA must engage in scientific analyses to determine what type of food labeling is most useful to consumers who want to make healthy choices.

- *Understanding the risk of toxins*

As they develop and grow, infants and children need to be protected from exposure to dangerous levels of toxins in the foods they eat, the medical products they use and other products they come into contact with. FDA's National Center for Toxicological Research is committed to identifying these toxins and reducing the risk of adverse health effects from products on the market.

As the makeup of products becomes increasingly complex, so too must science at the FDA adapt to meet these challenges.

III. PROTECTING AGAINST EMERGING INFECTIOUS DISEASES AND TERRORISM

Infectious diseases know no boundaries. Our world is faced with constantly emerging and naturally occurring new threats, from pandemic influenza to novel pathogens like the SARS coronavirus. Simultaneously, we must be cognizant of the fact that our world is unstable; thus, we are susceptible to chemical, biological, radiological, and/or nuclear attacks as well. We must prepare for a broad range of potential threats, both natural and deliberate — from anthrax to smallpox to influenza to something new or unexpected. Moreover, major, devastating infectious diseases, such as TB and malaria, and even common bacteria such as *Staphylococci*, are increasingly resistant to available treatments, threatening people in all nations.

Current approaches to the development and evaluation of needed vaccines, diagnostics and treatments are not sufficient to quickly and fully meet global and domestic needs. The development of these needed medical countermeasures (MCM) has yet to take full advantage of scientific innovations in basic science or in product development — manufacturing and evaluation that could transform preparedness and redefine global health.

What has FDA done?

For years, FDA has been central to the identification and development of vaccines to protect against each new strain of influenza on an annual basis. A successful public-private partnership during the 2009 H1N1 influenza pandemic brought about the development and approval of safe and effective vaccines in record time. These and the more detailed example below are a few examples of regulatory science efforts ongoing at the FDA.

- *Prevented contamination of the nation's blood supply*

West Nile virus is an illness spread by mosquitoes which results in asymptomatic infection, fever, meningitis or encephalitis and/or death. In 2002, a total of 4,156 cases of West Nile virus infections were reported. This number more than doubled to 9,862 in 2003, before gradually tapering off to 720 cases in 2009. FDA and CDC were also concerned that the virus could potentially be transmitted via blood transfusion and organ transplantation. In September 2002, such transmission was confirmed. As the health care system worked to treat those infected with the potentially

deadly disease, FDA worked intensively with CDC and the blood and diagnostics industries to rapidly respond to the threat to blood safety, including employing strong regulatory science to develop the standardized reagents needed for test development. This effort was pivotal in supporting the rapid nationwide implementation of blood donation testing for West Nile Virus and helped ensure that the nation's blood supply remained safe, preventing a potentially serious epidemic of transfusion transmitted infection.

What can FDA do with increased investment in regulatory science?

A committed, continuous investment in regulatory science is essential to producing medical countermeasures against public health threats. As noted in the Public Health Emergency Medical Countermeasures Review, "Enhancement and ultimate application of updated regulatory science and scientific review capacity will help strengthen the MCM regulatory process and thus streamline the MCM development process. FDA will undertake a new initiative ... designed to focus on augmenting the tools used to assess the safety, efficacy, and quality of medical products, with a particular focus on MCMs, and to get them from concept through the approval process efficiently."

We need these investments to resolve outstanding scientific issues and to create efficient regulatory pathways for new products, especially where market incentives are lacking or unpredictable. Two specific areas of critical need are (1) the development of better ways to assess product efficacy and (2) the availability of new technologies that can be used more nimbly and rapidly to address multiple, even unknown, threats. Listed below are some ways FDA can use regulatory science to protect the public's health.

- *New approaches to evaluate product efficacy*

It is not always possible to test whether a vaccine or treatment will work against a new or emerging infectious disease, or against a terrorist threat, because the threat may be rare — or even nonexistent — at the time the therapy needs to be developed. Animal testing is often the only available option, but many diseases lack even good animal models, and animal studies are technically difficult to conduct and typically limited in size. Therefore, regulatory science is needed to develop and validate improved predictive models.

Regulatory science can also support the identification and validation of surrogate measures of product efficacy. For example, FDA's definition and acceptance of a serum hemagglutination inhibition antibody titer, which helps predict the efficacy of influenza vaccines, took years off the time required to approve new flu vaccines, and, as a result, helped to double the number and capacity of U.S. licensed flu vaccine makers. Such *biomarkers* (e.g. responses in blood tests, other measurements, or medical images) that predict efficacy are not yet available for most terrorism threats, emerging pathogens or major global infectious diseases. Efforts to develop, refine and validate new biomarkers can lower development costs and improve and speed the development of safe and effective products for unmet public health needs.

- *More flexible and agile approaches to product development and manufacturing*

Knowledge of genetic sequences can enable us to produce products such as DNA and recombinant vaccines, or needed treatments and diagnostic tests, more quickly and safely without using the pathogen in manufacturing.

The use of *platform* technologies of this sort may offer the potential to scale up production more rapidly. For example, several technologies could potentially allow production of large amounts of new

influenza vaccines for a pandemic in weeks, rather than months. Platform technologies may also be applicable across broader ranges of products. For example, the same virus-like particle, live vector, DNA vaccine or recombinant protein expression system could be used as the basis to rapidly develop and produce different, distinct vaccines intended to protect against illnesses such as flu, plague, SARS or TB. Even stronger commonalities apply across technologies that can be used for detection or diagnosis, such as high-throughput assays for antibody, antigen and nucleic acid detection.

Evaluating such multi-use technologies and products requires advances in regulatory science — including new methodologies for measuring product quality, potency, safety and effectiveness. FDA guidance and engagement with partners will be critical to make sure products can move from the future into the present.

- *Validation of improved potency and rapid sterility assays*
Modernized, rapid testing methods are needed to support more rapid deployment of life-saving products in an emergency. FDA must work to develop and implement rapid, sensitive, high throughput methodologies to detect, identify and investigate microbial or other product contaminants to elevate the nation's public health preparedness to emerging infectious diseases and other natural or man-made threats.
- *Methods to improve product stability*
Regulatory science can be applied to find ways to enhance the shelf life of products or to avoid the need for cold storage, which is required for many drugs and vaccines. These improvements may be of critical importance in an emergency and are important cost-saving tools for fighting disease globally.
- *New statistical approaches to assessing efficacy where data is limited*
Just as laboratory sciences have advanced, biostatistical approaches are rapidly evolving. New methods that provide reliable information from more limited data sets can be crucial during an emerging disease outbreak.
- *Cell culture and in silico modeling of safety and efficacy*
The ability to predict safety or efficacy in a test tube or in *silico*, through computer modeling can save time and resources; may result in safer, more targeted therapies; and is critical when a disease is rare or when there is insufficient time to complete clinical trials.
- *New point-of-care diagnostics*
Application of novel technologies, such as nanotechnology, is needed to enhance our ability to detect and diagnose disease at the point of care during an emergency. This could also enable development of tests to immediately detect drug resistance during a public health emergency, so that patients are sure to get treatment that works.
- *New dosing forms and delivery methods*
Response time in an emergency can be everything. New product formulations and deliveries, such as needle-free systems, are needed for more nimble distribution and use of products and to allow their self-administration, where appropriate.
- *Real-time assessment of product performance*
Application of information technology tools, advanced biostatistics methods and health data mining are needed to assess product effectiveness and safety during emergencies. The unprecedented

safety monitoring systems put in place for 2009 H1N1 vaccination program were an example of real-time assessment in action. FDA should work to develop a bioinformatics database for emerging infectious diseases that are potential threats to the blood supply.

- *Enhanced risk assessment and communication*

Advances in the science of risk assessment and risk communication are needed to provide clear, accurate and understandable information to the public, enhance public confidence and empower people to make wise decisions and protect their health and their communities.

IV. ENHANCING SAFETY AND HEALTH THROUGH INFORMATICS

FDA houses the largest known repository of clinical data — unique, high-quality data on the safety, efficacy and performance of drugs, biologics and devices, both before and after approval. But despite the availability of these data, questions about subpopulation responses and underlying placebo effects remain unanswered. FDA data could be used to address fundamental questions about patient subsets who respond in varying ways to new therapies, or for whom a drug is more or less safe. But we lack the right infrastructure, tools and resources to organize and analyze these large data sets across the multiple studies and data streams. In other words, we have a valuable library full of information, but no indices or tools for translation.

What has FDA done?

FDA has been investing in the infrastructure necessary to support receipt of study data electronically and to develop an environment conducive to analyses of large data sets. This dedication to creating a scientific computing environment in which multiple studies can be compared and analyzed requires data harmonization and standardization such that comparisons between data can be made effectively. FDA has participated in efforts and initiated pilot projects to begin aligning its systems to the Health Information Technology (HIT) standards that are part of the national effort to develop a system to support electronic health records. Clearly, in a world of accumulating data and information, FDA remains in pursuit of systems and approaches to house and analyze its vast data stores and ever increasingly complex data arriving daily. As noted below, engagement in standards activities is one of several activities devoted to health information technology for assessing products both pre- and post-market.

- *Clinical Data Interchange Standards Consortium (CDISC)*

In 1997, CDISC began as a group of 25 individuals, including representatives from FDA, pharmaceutical companies and vendors. These volunteers came together to support the development of standards that could be used in clinical trials to improve the ability to collect and analyze data across industry and academia, without bias towards any one sponsor or organization. These standards enable better and more efficient safety and effectiveness data analysis and faster evaluation of important new medications. CDISC has evolved into a not-for-profit organization with hundreds of participants from around the globe and has produced a number of data-production standards including the Study Data Tabulation Model (SDTM), a standard used for submitting electronic safety and clinical data to FDA. *(In November 2009 the FDA announced that it will accept submission in SDTM version 3.1.2)*

What can FDA do with increased investment in regulatory science?

The vast data stored at FDA must be transformed into a harmonized format and organized in a common database so that it can be queried by topic and analyzed to address key questions. These goals require investments in informatics hardware and software and the development of standardized data models for relational databases and scientific computing.

With a common platform in place, scientists could take advantage of existing historical data as well as the new data coming into FDA every day. For example, we would be able to look at 15 studies of HIV drugs at once to analyze which drugs work best for which patients and when or use the data to detect a new or rare safety risk by capturing safety information from millions of medical records in months instead of years. These types of analyses will not only enhance review by applying lessons learned from one study to another but also provide incredibly valuable information about diseases and therapies, along with unprecedented insight into the mechanisms that govern their successes or failures. These insights will benefit FDA and the biomedical and healthcare community at large, enabling physicians to make more informed decisions about the optimal use of FDA-regulated products.

A better understanding of the natural history of disease and the effects of specific interventions should make clinical development and evaluation of new products more efficient and quick and less costly and risky for patients. There are many areas for advancements:

- *Real time monitoring of safety data using healthcare data*

We need to expand and harmonize our electronic systems for receiving, processing, storing and analyzing adverse event reports and other safety information for FDA-regulated products, while at the same time ensuring we protect patient privacy. The database requires a portal through which external users can easily submit data to FDA for organization and analysis. (This system should ultimately be able to communicate with the Sentinel System, which is in development and will provide active surveillance for monitoring post-approval product safety using electronic data from healthcare information holders such as HMOs and other health systems.) Additional investments to capture healthcare and other related surveillance data are also needed — as is continued collaboration with agencies like the Centers for Medicare & Medicaid Services (CMS) and the Department of Defense — to develop a system that can provide ongoing, accurate, real-time information about the safety of therapies in different patient subpopulations. Similarly, we require investments in infrastructure to support these complex and interconnected data systems and to promote development of electronic data standards to facilitate electronic submissions of readily interpretable sponsor data.

- *Data mining and scientific computing*

Investments in new software tools are needed, as are collaborative projects that bring together the latest technologies and approaches for mining complex data from clinical trials, healthcare settings and biological studies. These approaches will not only enhance review quality and efficiency but also provide FDA with knowledge that can move product development toward personalized medicine. Some key areas for focus for scientific computing include but are not limited to the following:

- *Develop and implement active post-market safety surveillance system that queries health system databases to identify and evaluate drug safety.*
- *Expand PRISM (Post-Licensure Rapid Immunization Safety Monitoring) System to other vaccines and biologics.*
- *Employ advanced informatics, modeling and data mining to better detect and analyze safety signals.*
- *Apply computer-simulated modeling to risk assessment and risk communication strategies that identify and evaluate threats to patient safety; develop methods for quantitative risk-benefit assessments.*
- *Enhance IT infrastructure to support the scientific computing required for meta-analyses and computer models for risk assessment.*

- *Apply clinical trial simulation modeling and adaptive and Bayesian clinical trial design methods to facilitate development of novel products.*
- *Apply human genomic science to the analysis, development, and evaluation of novel diagnostics, therapeutics, and vaccines.*
- *Apply appropriate statistical analysis of genomic studies.*

Partnerships with academia, industry, and other governmental agencies are an important part of the equation. These efforts, with new paradigms for clinical trial design and surveillance of all FDA regulated products, will enhance patient outcomes and bring FDA fully into the 21st century.

V. PROTECTING THE FOOD SUPPLY

Food safety is one of FDA's most critical public health priorities. As in other areas, the effectiveness of FDA's food safety program depends on the strength and capacity of the science underlying it. Although much research on food safety is carried out at universities and in private industry, FDA's regulatory role creates unique scientific and technological needs and opportunities that can be met only by a robust regulatory science program.

In 2007, FDA's Science Board warned that a lack of adequate scientific capacity and tools in FDA's Foods Program was limiting the agency's ability to protect the nation's food supply.

What has FDA done?

To meet the challenges of the 21st century food supply, including the dramatic increase in imported foods, FDA has increased its investment and sharpened its focus on the science needed to detect food safety breakdowns and to understand how they occur. Although the ultimate goal is to prevent food safety breaches from occurring in the first place, we need the tools to contain them effectively and efficiently if they do occur. As noted in the example below, these technologies are critical on an ongoing basis and in the event of natural disasters that affect the food supply.

- *Development of new chemical tests to assess food safety in the Gulf of Mexico after the Deepwater Horizon Oil Spill*

The Deepwater Horizon disaster released in excess of 92 million gallons of oil into the Gulf of Mexico, resulting in devastating environmental damage and concerns about the safety of seafood caught in that area. FDA, in concert with state health authorities, was and continues to be responsible for ensuring the safety of seafood caught in the Gulf. This is accomplished through extensive sampling and testing of seafood harvested from the Gulf and sampled from seafood processing and distribution centers across the nation. At the outset of the spill, a chemical method for measuring for the presence of polycyclic aromatic hydrocarbons (PAH), which are found in significant amounts in crude oil and which contain a number of known carcinogens, was known but required extensive time and effort for sample processing and analysis. The FDA worked diligently to develop a rapid, highly sensitive chemical testing method and is now using this method to test seafood from the Gulf to ensure it is safe for consumption.

What can FDA do with increased investment in regulatory science?

A major focus of FDA's interest in regulatory science is the development of more rapid and practical methods for detecting microbial pathogens in food and equipping FDA's labs to test multiple food samples for contaminants simultaneously. FDA must also provide scientific leadership to enhance understanding of the causes of food borne illnesses so that interventions can be designed and implemented to effectively and feasibly reduce risk.

A number of additional opportunities exist to advance regulatory science to improve food safety:

- *Developing effective tools and strategies for sampling, testing and analysis*
Tools for the laboratory and for field investigators, such as hand-held devices, are being developed and evaluated to enhance analytical capacity and capability for detecting pathogens of major public health concern such as *E. coli* O157:H7, *Salmonella*, and *Listeria*.
- *Tracking salmonella in the food supply*
Salmonella is the leading bacterial cause of food-borne illness in the United States and can originate from many different animal sources. Rapid methods are being developed to speed the detection and investigations of outbreaks. We are using cutting-edge technology to investigate and identify animal sources for human *Salmonella* infections, as well as antimicrobial resistance and virulence determinants.
- *Preventing microbiological hazards*
FDA is studying the prevalence and behavior of microbiological hazards in foods to provide the data needed to assess risks, determine the effectiveness of potential control strategies, establish food safety standards and provide practical food safety guidance to industry.
- *Responding to food-borne illness*
Identifying virulence factors, epidemiological markers and other determinants that influence the ability of pathogenic microorganisms to use foods as vehicles for disease transmission will help enhance epidemiological investigations, intervene earlier in an outbreak and more accurately attribute illness to a product.
- *Controlling toxins*
FDA is attempting to identify the effect of food production, processing, preparation and use practices on the generation of toxic contaminants, inactivation of naturally occurring toxins and nutrient content.
- *Monitoring antibiotic resistance in food-borne pathogens*
Ongoing monitoring of antibiotic resistance is central to FDA programs to limit the spread of antimicrobial-resistant food-borne pathogens. The National Antimicrobial Resistance Monitoring System (NARMS) monitors trends in antibiotic resistance among food-borne pathogens from animals (conducted by the U.S. Department of Agriculture), humans (conducted by the CDC) and retail meats (conducted by FDA). Since its inception in 1996, more than 210,000 test results have been added to the NARMS database. All NARMS recovered *Salmonella* and *Campylobacter* isolates are compared to human isolates in CDC's PulseNet database. Expansion of this effort could provide additional critical information about the effect of antibiotic use in animals on resistance in human bacterial strains.

With continued and enhanced efforts in these and other areas of regulatory science, FDA can help provide the knowledge, tools, and scientific leadership needed to improve food safety and protect public health.

VI. MODERNIZING SAFETY TESTING

For more than a century, toxicology has largely relied on animal testing. Such testing, however, is costly and time consuming and does not always provide results that reliably correlate with human

responses. As a result — and out of concern and respect for animals — we must develop methods for safely reducing, refining, or replacing animal testing. This requires development and validation of methods that are reliable in predicting safety and other product attributes. Advances in life sciences and engineering are ushering in the potential to dramatically change the way toxicology assessments are performed, but these new technologies have not yet been sufficiently studied or tested. Investments today can help seed a revolutionary change in toxicology and hazard assessment.

What has FDA done?

One of the cornerstones of safety assessment at the FDA is the National Center for Toxicological Research (NCTR) which is responsible for conducting FDA mission-critical, peer-reviewed, critical path (translational) research to develop a scientifically sound basis for regulatory decisions and reduce risks associated with FDA-regulated products. This research is aimed at evaluating the biological effects of potentially toxic chemicals or microorganisms; defining the complex mechanisms that govern their toxicity; understanding critical biological events in the expression of toxicity; and developing methods to improve assessment of human exposure, susceptibility, and risk.

As illustrated in the example below, each product center within the FDA is also engaged in research efforts to develop new tools and standards for evaluating safety of new drugs, biologics, or devices.

- *Novel kidney biomarkers for preclinical toxicity studies*

Unfortunately, new drug candidates often fail late in development after significant investments have already been made toward their development. It is critical to identify potential safety issues as early in the development process as possible, before human studies are performed. Some of the most common toxicity problems occur in the liver, kidney, or cardiovascular system. In recent years, FDA, working with the European Medicines Agency (EMA), has led several collaborative efforts that have brought together these agencies with academic and industrial groups in consortia, seeking to identify and qualify novel biomarkers for detecting drug-induced kidney toxicity in preclinical animal models. Recently, FDA and EMA endorsed a number of these biomarkers, originally detected and identified using microarrays. These biomarkers provide a non-invasive strategy for detecting kidney toxicity in animal models and are more sensitive and specific than traditional tests. Additionally, these markers may prove to be an effective monitoring tool for kidney toxicity in human studies. (Predictive Safety Testing Consortium <http://www.c-path.org/pstc.cfm>)

What can FDA do with increased investment in regulatory science?

Initial regulatory science investments would be aimed at bolstering new technologies — specifically, biomarkers for better risk protection — to improve both animal and non-animal models and create bridges between them. For example, data from cell culture methods, genomics microarrays, as well as proteomics and metabolomics should be expanded and correlated with both animal testing results and experience from human clinical studies. The goal would be to replace or refine exposure experiments with predictive markers. Investments in analysis of large sets of data would provide valuable information for understanding how classes of chemicals cause toxicity. These approaches require new instrumentation, platforms, and databases, and training for FDA scientists to enable them to use and interpret data from these approaches. Collaboration with academia, industry and sister government agencies will be critical.

Another related and important area for advancing regulatory science is to increase the use of in vitro and, potentially, computer-based modeling systems for toxicology. The development of cell lines, engineered model tissues and other cell culture approaches will be critical, not only to better

understand underlying mechanisms triggered in human cells following exposure but also to replace current approaches with more efficient and cost-effective toxicology studies.

The increasing deployment of new and complex technologies, such as nanotechnology, also creates the need for new approaches and methods to better evaluate, understand, and predict the potential toxicity of these materials. For all FDA regulated products, from foods to medicines, we must improve methods and models to assess and effectively communicate both risks and benefits to support sound regulatory decision-making, empower consumers and — above all — protect the public health.

VII. MEETING THE CHALLENGES FOR REGULATING TOBACCO

The recently passed Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) grants FDA the authority to regulate the manufacture, marketing, and distribution of tobacco products. The Center for Tobacco Products (CTP) was created to lead this effort by harnessing the best available science to guide the development and implementation of effective public health strategies to reduce the burden of illness and death caused by tobacco products.

The Tobacco Control Act gives the CTP important authorities, including restricting the marketing of tobacco products to children and youth, requiring new warning labels, and prohibiting marketing measures that are misleading to consumers. It also requires CTP to:

- *Require industry reporting of tobacco product ingredient and constituent data, including a description of the nicotine content and delivery mechanisms.*
- *Establish tobacco product standards.*
- *Require good manufacturing practice standards for tobacco product manufacturing facilities.*

What can FDA do with increased investment in regulatory science?

There are several ways in which advances in regulatory science can enhance CTP's success in regulating tobacco products and protecting the American people from their dangers:

- *Biomarkers for tobacco-associated pathogenesis and disease*
Tobacco products contain thousands of toxic constituents, but knowledge about the link between specific constituents and specific diseases is still evolving. CTP will need to be able to evaluate the relative contribution of each of these toxic constituents and their potential to cause disease. Since tobacco-related diseases are caused by chronic exposures that occur over years, even decades, CTP will have to work with the research community to develop and test biomarkers that can be linked to specific tobacco-related disease risks. This, in turn, will enable CTP to determine scientific bases for guidelines and review criteria for tobacco products, including industry claims of substantial equivalence, applications for non-equivalent new products, and applications for products claiming to provide reduced risk of harm.
- *Tobacco product standards*
The law gives FDA authority to set performance standards for tobacco products, standards that may help make entire classes of products less addictive or less harmful. Successful development and implementation of these standards will depend on the development of a strong science base.
- *Tobacco product advertising and marketing*
FDA can propose and implement targeted restrictions on advertising and marketing — particularly those targeted to children and youth — to reduce initiation of tobacco use. Recognizing which

industry activities have the greatest effect on youth smoking can help the agency design regulatory efforts to block them. Measuring the effects of these actions on initiation will ensure that FDA is able to meet its goals.

FDA will work with a broad range of experts and engage the academic community to move this field forward. In these and other areas, progress in regulatory science can enhance CTP's ability to attract, recruit, and retain the review, laboratory, and population scientists needed to achieve its mission and, ultimately, mean the difference between actions that are ineffective and actions that save lives.

A COLLABORATIVE IMPLEMENTATION FRAMEWORK

FDA has outlined a four-part strategic framework to lead the nationwide effort to advance regulatory science within the agency and around the nation — and deliver the benefits to the public.

- *Leadership, coordination, strategic planning, and transparency to support science and innovation*
- *Support for mission-critical applied research, both at FDA and collaboratively*
- *Support for scientific excellence, professional development, and a learning organization*
- *Recruitment and retention of outstanding scientists*

Each part of the plan includes activities that will strengthen FDA's scientific capacity and promote collaboration with partners in government, industry and academia. Ultimately, this plan should result in organized and tangible efforts to bolster the field of regulatory science globally and promote new and — above all — creative approaches to product development and safety for both food and medical products.

I. Leadership, coordination, strategic planning, and transparency to support science and innovation

The Office of the Chief Scientist will coordinate internal and external outreach to identify critical regulatory science and innovation needs and develop a strategic plan for science at FDA. Within the chief scientist's office, the Office of Science and Innovation will develop the strategic plan, track the outcomes of our investments, organize cross-center scientific collaborations, and monitor outside partnerships.

Key input will be provided by:

- *The Science and Innovation Strategic Advisory Council*

Internally, FDA has formed a high-level advisory board comprising the Chief Scientist and key senior leadership from the Office of the Commissioner, the centers, and ORA. This board will meet at least twice yearly to identify and communicate key scientific priorities from each center, to help set and discuss major cross-cutting scientific priorities for the agency, and to propose and evaluate major programs and partnerships. This input will help drive the strategic science plan.

- *The FDA Science Board*

The FDA Science Board is already in place to provide advice to the Commissioner, the Chief Scientist and the centers on FDA's scientific programs and on complex scientific and technical issues within the agency, industry, and academia. The Science Board will be asked to periodically review and inform the scientific strategic plan and regulatory science priorities proposed by the Science and Innovation Strategic Advisory Council and the Chief Scientist.

II. Support for mission-critical applied research, both at FDA and collaboratively

Support within the FDA is critical to expanding the field of regulatory science. An active research program, directly connected to the FDA review process, will not only bring needed advances in regulatory science straight to FDA review, product development, and evaluation but will also add value to guidance and policy development.

In addition, the discipline of regulatory science must be developed through support from both partnerships and external research and collaboration. There are substantial opportunities to enhance and expand current FDA programs and to develop new ones that support effective, more robust, external and collaborative efforts to advance regulatory science. Some projects are already under way:

- *A **Joint Leadership Council** recently created by FDA and NIH to promote the expansion of regulatory science through enhanced scientific collaboration and jointly supported and administered extramural research grants in regulatory science.*
- *Creation and support of academic **Centers of Excellence in Regulatory Science** to carry out applied regulatory science research both independently and in collaboration with the FDA and as a locus for scientific exchange and training opportunities for both FDA and academic scientists*
- *Enhanced strategic collaboration and coordination with other governmental agencies to develop new programs to advance regulatory science and innovation*
- *Enhanced support and focus for the **Critical Path Initiative** to catalyze and enable partnerships and consortia that advance regulatory science and public health through innovation and modernization of the medical product development and evaluation process*
- *Partnership with the **Reagan-Udall Foundation** on projects in support of regulatory science*

III. Scientific excellence, professional development, and a learning organization

FDA will support a culture of and capacity for continuous scientific learning and professional development of our scientific staff. The agency will explore several approaches:

- *Access to cutting-edge, continuing education and professional development for FDA staff — through universities and government agencies, for example — as well as policies and resources that support these activities*
- *Scientific exchange programs with academic and governmental institutions and with international regulatory counterparts*

IV. Recruitment and retention of outstanding scientists

FDA will seek to recruit and retain an outstanding scientific workforce that is engaged from its laboratories to its review teams, and that is up to date with new and emerging technologies. The Commissioner's Fellowship program has begun to attract, train, and recruit promising young scientists in key areas of science, innovation, and review and has enriched the FDA environment. FDA will consider other approaches:

- *A program to help recruit and support promising newly independent scientists expert in emerging technologies to be researcher-reviewers throughout the FDA*

- *Proposed merit awards, which will be competitively awarded to support the most accomplished and productive FDA scientists to continue their work at FDA*
- *Proposed FDA Expert Physician Program to support joint part-time, academic faculty/FDA positions to benefit from expertise in cutting-edge patient care and from improved perspectives in regulatory review, particularly for areas of emerging technologies. Participants, thoroughly screened for conflicts of interest, would spend time working with full-time FDA staff in review and policy activities.*

Support for these four approaches will develop and advance the field of regulatory science to help provide the tools and the knowledge required to realize the promise of innovation. These efforts will help us bridge the gap from basic science discoveries to safe, effective products that help patients, protect health and security, enhance the safety of our medicines and foods, and support innovative, effective medicine and public health.