The Critical Path Initiative

Projects Receiving Critical Path Support in Fiscal Year 2008

Department of Health and Human Services
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Introduction

The Critical Path Initiative (CPI) is the Food and Drug Administration's national strategy for modernizing the sciences through which FDA-regulated products are developed, evaluated, manufactured, and used. The Initiative was launched in March 2004 to address the steep decline in the number of innovative medical products submitted for approval, despite the enormous breakthroughs being made in biomedical science. Although initially conceived as a drive to apply discoveries in emerging areas of science and technology to medical product development, the Initiative has since expanded its scope to include all FDA-regulated products.

Background

The Critical Path Initiative (CPI) was launched in March 2004, with the release of FDA's landmark report *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*.[1] The publication diagnosed the reasons for the widening gap between scientific discoveries that have unlocked the potential to prevent and cure today's biggest killers and their translation into innovative medical applications.

Sounding the alarm on the increasing difficulty and unpredictability of medical product development, the report concluded that collective action was needed to modernize scientific and technical tools—like in vitro tests and innovative study designs—and harness information technology to evaluate and predict the safety, effectiveness, and manufacturability of medical applications. The report called for a nationwide effort to identify specific activities all along the critical path of medical product development and use, which, if undertaken, would help modernize the critical path sciences.

In March 2006, the Secretary, Department of Health and Human Services (HHS), and FDA's Commissioner announced the release of *FDA's Critical Path Opportunities Report and List*.[2] The List, which was developed with broad contribution from the public, described areas in which the product development sciences had the greatest need for improvement.

It listed 76 tangible examples of areas where new scientific discoveries—in fields like genomics, imaging, and bioinformatics (the analysis of biological information using computers and statistical techniques)—could be applied during development to improve the accuracy of tests that predict the safety and efficacy of potential medical products.

Following the report's release, FDA launched a major drive to facilitate collaborations with all stakeholders to tackle identified issues. During 2006 and

[1] The 2004 Critical Path report is available at http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.pdf.
[2] This report can be found at http://www.fda.gov/oc/initiatives/criticalpath/reports/opp_list.pdf.

2007, numerous innovative projects were undertaken as part of CPI. The Critical Path Web page hosts the 2006 and 2007 reports on projects launched each year.

CPI's Widening Scope

Globalization, rapidly-evolving technologies and emerging areas of science are having an increasing impact on all FDA-regulated products. Therefore, CPI has gradually expanded its scope, leveraging the knowledge gained from new scientific fields to enhance the tools FDA uses to evaluate veterinary products, food, and food ingredients (e.g., new rapid tests to determine biological and chemical contamination of animal-derived foods). Complex new technologies such as genetically engineered plants and animals, and cloning are bringing new challenges to veterinary medicine that require sophisticated cross-disciplinary scientific evaluation.

In another area, novel bioinformatics approaches are making it possible to put in place the cutting-edge information systems that are critical to supporting medical innovation and public health safety. Critical Path projects described in this report highlight efforts by FDA and its collaborators to move toward a flexible, fully integrated electronic infrastructure that is capable of receiving and managing crucial product data in real time. These projects are streamlining the information tracking systems for all Agency-regulated products, including adverse events reporting and tracking human and animal food contaminations.

CPI has become the main engine driving FDA's push for innovation, that is, to facilitate the development of 21st century methods of monitoring food and medicines and approaches to treatment. For the first time, in 2008, Congress funded the Initiative directly. Some funding went straight to FDA's centers; some funding went to the Office of Critical Path Programs (OCPP) in the Office of the Commissioner to support FDA Critical Path projects. This report briefly describes the projects that have received support through the Critical Path Initiative during fiscal year 2008.

Critical Path Initiative
Projects Receiving Critical Path Support During Fiscal Year 2008

FDA's Critical Path Initiative (CPI) has become the main engine driving FDA's push to develop 21st century tools and methods for monitoring food, medicines and treatment approaches. In 2004, CPI was launched to create a framework for stimulating efforts to modernize the development, evaluation, manufacture and use of medical therapies and other FDA-regulated products. In 2008, for the first time, Congress funded CPI directly. Some of this funding went to FDA's centers to support Critical Path projects; some went to the Office of Critical Path Programs (OCPP) in the Office of the Commissioner for the same purpose.

This 2008 activities list briefly describes more than 50 scientific projects undertaken with participation of FDA centers and offices that received Critical Path support from congressionally appropriated funding during fiscal year (FY) 2008. All projects involved FDA participation, and all but a few described in this report are linked directly to the six Critical Path Priority Topics described in FDA's March 2006 publication *Critical Path Opportunities Report and List*:

(1) Developing Better Evaluation Tools
(2) Streamlining Clinical Trials
(3) Harnessing Bioinformatics
(4) Moving Manufacturing into the 21st Century
(5) Developing Products to Address Urgent Public Health Needs
(6) At-Risk Populations—Pediatrics

This report groups project descriptions by organization (e.g., office or center), to reflect the way funding was distributed and used. Consistent with the CPI focus on collaboration, many of the projects involve partnerships among FDA centers and between FDA and other organizations, including other federal agencies, academic organizations, patient advocacy groups, and industry. A list of organizations participating in CPI projects is available upon request.

Many of the projects described here have been under way for a year or more and may have appeared in previous CPI activities lists. To the extent possible, the projects have been described in lay language.

FDA's Office of Critical Path Programs

The Office of Critical Path Programs (OCPP), in FDA's Office of the Commissioner, was created in 2004 following the launch of the 2004 Critical Path Initiative (CPI) to provide central coordination for the initiative; lead certain Agency-wide CPI projects; support CPI projects in the centers with funding, staffing, and/or project management expertise; and direct Critical Path-related communication efforts, both internal and external to the Agency.

In addition to leading some CPI scientific or technical projects, the OCPP develops and publishes most CPI-related reports, interviews, and other updates. The OCPP maintains the Agency's CPI Web site[3], receiving and triaging public inquiries to it. The OCPP also supports the activities of the FDA-wide Critical Path Steering Committee. The Committee meets monthly to coordinate its Critical Path Rounds[4] and other efforts as well as share scientific and technological information on ongoing and planned activities.

The OCPP is currently leading a number of Critical Path projects that have broad Agency participation. These projects are described here.

1. Establish a nationwide system for monitoring postmarket safety of regulated products

Challenge: An important part of FDA's mission is to protect public health by monitoring the safety of medical products and other FDA-regulated products once they are on the market. FDA currently has a number of reporting systems in place for tracking reports of adverse events and understanding product problems associated with the use of FDA-regulated products. Most of these systems are passive; someone (e.g., healthcare professionals, consumers, pharmaceutical companies) must first report such an event to the FDA.

Project: Develop the Sentinel System, a national, distributed, electronic system designed to enable FDA to actively monitor the safety of drug and biological products, medical devices and, ultimately, all FDA-regulated products.

To transform FDA's current, mostly passive, safety monitoring systems, FDA launched the Sentinel Initiative in May 2008. The Initiative's goal is to develop a system that will enable FDA to leverage the capabilities of multiple, existing electronic healthcare data systems (e.g., electronic health record systems, administrative claims databases, registries) to actively monitor medical product safety.[5] As currently envisioned, this system, called the *Sentinel System*, would enable FDA to query remote data owners quickly and securely for

[3] See the Critical Path Web site at http://www.fda.gov/oc/initiatives/criticalpath/.

[4] The Critical Path Rounds was launched in 2009 to facilitate information-sharing among FDA employees on the various projects under way in FDA centers. Rounds occur every other month as part of the Critical Path Steering Committee meetings and are open to all FDA staff.

[5] This project is being overseen by FDA's Bioinformatics Board, an Agency-wide board, whose role it is to ensure a coordinated approach to information technology efforts at FDA.

relevant product safety information. (Data will continue to be managed by its owners.) Questions would be sent to the appropriate, participating data holders, who in turn would, in accordance with existing privacy and security safeguards, evaluate their data and send summary results to FDA for further Agency analysis. This system will be developed and implemented in stages. It is expected to facilitate the development of active monitoring methodologies related to signal detection, signal strengthening, and signal validation.

The Sentinel System's scope and complexity requires the broad participation of many stakeholders for the system's success. Since announcing the Initiative, FDA has fostered a wide public forum to explore the multifaceted challenges of creating such a system. Numerous meetings have been held with a variety of stakeholders. Eight contracts have been let to explore the myriad issues raised by Sentinel, and a number of pilot projects are under way that will contribute to answering the technical and policy issues that must be resolved. FDA expects that 2009 will see the development of a viable governance model for the organization that ultimately will oversee Sentinel's creation and implementation.

Project Collaborators: FDA is heavily involved in various types of partnerships and collaborations with stakeholders to explore technical and policy issues that ultimately will inform the Sentinel System. In addition, a number of pilot projects have been initiated in the FDA centers to evaluate Sentinel's technological and methodological issues. For more information on efforts under way, see FDA's Sentinel Web page.[6]

2. Modernize the clinical trial enterprise

Challenge: Patients and those who care for them want access to new drugs, devices, and biological products as quickly as possible, while also being sure that the benefits of these products outweigh the risks. Randomized clinical trials are the most reliable way to get unbiased information. However, the current system of conducting clinical trials is often paper-based, slow, and costly, draining precious resources from the development of innovative therapies.

Project: FDA and Duke University joined together as founding members of a public–private partnership, CTTI, to identify practices that through broad adoption will increase the quality and efficiency of clinical trials.

Clinical trials are a critical tool for determining which preventive, diagnostic, and/or therapeutic interventions have value and to compare alternative treatments. As the numbers and complexities of trials increase and as new technologies emerge and become more sophisticated, it is important to evaluate our current clinical trial system to ensure that it is functioning commensurate with the scientific and technical knowledge at hand. It is also critical to ensure that we maximize the safety and protection of trial participants. The clinical trial system's success will depend on continued public confidence in the system's safety, integrity, and transparency.

[6] The Sentinel Web page is at http://www.fda.gov/oc/initiatives/advance/sentinel/ and the Sentinel report can be found at http://www.fda.gov/oc/initiatives/advance/reports/report0508.html.

FDA and Duke University have joined together as founding partners of a consortium of concerned stakeholders, the Clinical Trials Transformation Initiative (CTTI), to undertake projects proposed by members and the public. CTTI's goal is to identify practices that through broad adoption have the potential to increase the quality and efficiency of clinical trials. *Quality* is characterized by the ability to effectively and efficiently answer the intended question about the benefits and risks of a medical product (therapeutic or diagnostic) or procedure, while ensuring protection of trial participants. This broad-based consortium[7] is examining current issues concerning the clinical trial enterprise and generating evidence to support the identification of best practices that will encompass the spectrum of clinical trials from study design and operating procedures to metrics for evaluation. CTTI's Executive Committee has approved two project concepts, which have developed into active projects:

- Improving the system for reporting serious adverse events to clinical investigators

This project will focus on unexpected serious adverse reactions (SAEs) that must be reported to clinical investigators who are managing clinical trials using the relevant product. The project will generate empirical evidence on resource use and on the value of the current system to increase the efficiency and effectiveness of informing investigators about safety events, thus, improving the protection of trial participants.

- Clinical trial monitoring

This project will benefit the clinical research enterprise by identifying best practices and providing sensible criteria to assist in selecting effective, appropriate trial monitoring while eliminating practices that may not be of value in ensuring reliable and informative trial data or trial participant protection.

Project Collaborators: FDA; Duke; and 46 representatives from other governmental agencies, academia, patient advocacy groups, contract research organizations, pharmaceutical, biotechnology, and medical device firms, and international organizations (a complete list of CTTI members is available upon request).

3. Expand and upgrade FDA's electronic adverse event and product problem reporting systems

Challenge: MedWatch, FDA's Safety Information and Adverse Event Reporting Program, is composed of multiple systems, many of which are more than 10 years old. Each FDA center maintains its own separate computer system to track adverse event and safety information about its specific products. These systems lack the analytic capabilities that are commonplace today; they also are not linked, making cross-product analyses difficult. Until recently, safety reports about dietary supplements and human food and pet food have been only voluntary, and the reports that are submitted come in a variety of ways, including by phone, fax, or standard mail.

[7] For more on CTTI, see http://www.fda.gov/oc/initiatives/criticalpath/clinicaltrials.html

Project: Modernize FDA's Medwatch system to encourage reporting and make it more efficient and effective.[8]

MedWatch, FDA's Safety Information and Adverse Event Reporting Program, serves both healthcare professionals and the medical product-using public. The program provides important and timely clinical information about safety issues involving medical products (e.g., prescription and over-the-counter drugs, biologics, medical and radiation-emitting devices, and special nutritional products, such as medical foods, dietary supplements and infant formulas). MedWatch provides information in a number of ways.

- Medical product safety alerts, recalls, withdrawals, and important labeling changes that may affect the health of all Americans are quickly disseminated to the medical community and the general public via FDA's MedWatch Web site and MedWatch E-list.
- The public can view select Safety Information (e.g., reports, safety notifications, and labeling changes) posted to the Web site.
- The MedWatch gateway enables healthcare professionals and consumers to report serious problems that they suspect are associated with certain FDA-regulated products (e.g., medicines, medical devices, blood products), but not all.

Reporting is done electronically, by phone, or by submitting the MedWatch 3500 form by mail or fax. Once received, reports are triaged to the appropriate system in the appropriate center.

MedWatch***Plus*** is the modernized version of MedWatch. Once implemented, it will be the single Internet portal to go to for reporting possible adverse events or product problems for all FDA-regulated products (including problems with foods or cosmetics, pet foods and veterinary drugs). MedWatch***Plus*** will consist of the following: (1) there will be a single electronic portal, or entry way, for the public to access the MedWatch program and submit electronic reports of product problems or suspected side effects of ***all*** FDA-regulated products; (2) to make reporting easier for the public, FDA (including all FDA centers)[9] and the National Institutes of Health (NIH) are collaborating on developing a standardized, Web-based electronic questionnaire, similar to a drop-down menu, to lead the reporting person through a series of questions to ensure that submitted information is complete; and (3) FDA is working to create FAERS, a new data repository for the submitted reports with up-to-date analytic capabilities (the eventual goal is to consolidate all existing reporting systems into FAERS). Eventually, MedWatch as we know it today will go away. MedWatch***Plus*** will be very different. It will enable healthcare professionals, patients, manufacturers, human and veterinary food processors, packagers, and transporters, just about anyone who comes in contact with any FDA-regulated product, to use the Internet to report a potential problem to the Agency in a timely and user-friendly manner. This new system will also enable the Agency to process that report efficiently and get it to the right place for analysis and regulatory action if action is needed.

Project Collaborators: FDA; NIH, Bethesda, MD; SRA International, Inc., Fairfax, VA.

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[8] This project is being overseen by FDA's Bioinformatics Board, an Agency-wide board, whose role it is to ensure a coordinated approach to information technology efforts at FDA.

[9] This project has been approved by FDA's Bioiformatics Board (BIB), which is overseeing implementation from an Agency-wide strategic perspective. Representatives from all Agency centers and numerous offices are closely involved.

4. Move FDA from a paper-driven to an electronic regulatory environment

Challenge: Existing and emerging technologies, including information technologies (IT), are making it possible for FDA to carry out its mission more efficiently and effectively.

Project: Create an environment in which FDA can electronically manage, communicate, and store the regulated product information it receives.

At FDA, *bioinformatics* means the design, development, and use of modern computer systems to efficiently and effectively manage the nation's regulatory, product information supply chain. Medical product information moves along this supply chain from product developer (data from phase 1, 2, and 3 development), to FDA (in the form of a marketing application), and, if the product is approved, to healthcare professionals and the consumer (in the form of the product's label and other use information). FDA relies on efficient management of this information to assess a drug's safety and effectiveness, as well as to communicate important safety information to the public. The current paper-based bioinformatics infrastructure that supports product information exchange is inefficient, and FDA is working to modernize it. Bioinformatics modernization requires improvements in three important information management domains: access, standards, and interface. We must have better access to information, more standardized information, and better interface with information (i.e., better tools to convert information into knowledge).

FDA's Bioinformatics Team, with members throughout the Agency, has been working with relevant stakeholders for more than a decade to develop and implement standards and systems to enable the electronic receipt, management, and storage of FDA-regulated product information (e.g., marketing applications, drug labels, and adverse event reports are now be submitted electronically), but this effort will take substantial time and money. With recent movement toward a universal electronic health record, it is more important than ever that FDA be able to take advantage of IT to carry out its mission. Many projects are under way at FDA. FDA's Bioinformatics Board (BIB), in the Office of the Commissioner, approves and oversees most information technology projects, and projects are cross-Agency efforts involving representatives from FDA centers and relevant offices. Some examples of projects that were led by staff in the OCPP during 2008 include:

- FIREBIRD/E-platform, part of FDA's effort to receive and manage information that is submitted to FDA (e.g., investigator information, information related to investigational and marketing applications)
- Janus, a pilot repository to manage and store clinical data[10]
- Drug establishment registration and drug listing, an electronic system, expected to be fully operational summer 2009, that will receive and manage key data on pharmaceutical manufacturing facilities and the medicines they produce[11]

[10] This project has been approved by FDA's Bioiformatics Board (BIB), which is overseeing implementation from an Agency-wide strategic perspective. Representatives from all Agency centers and numerous offices are closely involved.

- Multiple standards development activities

Project Collaborators: In addition to the FDA centers and offices, FDA is involved with a number of different stakeholders in these projects, including the National Cancer Institute, National Institutes of Health; CRIX, International; Health Level Seven; International Organizations for Standardization (ISO), Geneva, Switzerland.

5. Identify the possible genetic basis of adverse drug events

Challenge: As our understanding of pharmacogenetics grows and our ability to individualize treatments improves, we are finding that the presence of certain genes may indicate increased risk for a specific drug-related adverse event. The HLA-B 5701 gene as a biomarker for Abacavir toxicity is one example.

Project: Identify genetic markers that may indicate a patient is at risk for a specific drug-related adverse event.

CADRe (the Common Adverse Drug Reaction effort), a collaboration between FDA and the Critical Path Institute (C-Path), is working to identify genetic markers that may reveal those patients at risk for specific drug-related adverse events. Principles have been developed to assist with the selection of drug-related adverse events amenable to this approach. A preliminary list of candidate drug/adverse-event pairs has been compiled. C-Path is currently researching this list to select those adverse events that are most likely to have a genetic basis, based on medical literature and other sources. The HLA-B 5701 gene as a biomarker for Abacavir toxicity is being used as one example for this initiative. (Abacavir is an antiviral medication that prevents HIV cells from multiplying in the body.) Initial emphasis is being placed on adverse events with existing preliminary evidence of a genetic basis (e.g., Torsades de pointes (a potentially fatal disorder of heart rhythm caused by drugs that produce certain changes in the electrocardiogram, certain adverse events associated with newer antidepressants). A review of existing knowledge will identify areas for further study, possibly involving the testing of banked blood samples from patients who have already experienced these adverse events.

The initiative is an important step toward personalized medicine, enabling drugs to be used safely and effectively at the right dose in appropriate patients while preventing use in patients at risk for a bad reaction, or a poor therapeutic outcome.

Project Collaborators: FDA; Critical Path Institute (C-Path), Tucson, AZ.

[11] This project also has been approved by FDA's Bioiformatics Board (BIB.

6. Develop and implement an FDA training course for clinical investigators to deepen their understanding of the scientific, ethical, and regulatory issues in clinical research

Challenge: The clinical trial industry has a chronic shortage of trained, experienced clinical investigators committed to performing clinical trials over the long haul. The resultant need to continually recruit new investigators has consumed valuable resources and may compromise the quality of clinical research.

Project: Design, implement and launch an intensive three-day course aimed at forming a cadre of well-trained, seasoned clinical investigators.

Among the many challenges the clinical trial industry faces is a lack of experienced clinical investigators with the training, interest, and commitment to perform clinical trials. Statistics show that clinicians seldom continue as clinical investigators for longer than a few years.[12] The need to continually enlist new investigators drains resources and could compromise the quality of clinical research since new investigators may be less equipped to recognize emerging safety issues, ethical problems, and pitfalls in study design. They may also not fully apprehend FDA's regulatory and monitoring requirements.

To help develop a core of well-trained investigators, FDA's Office of Critical Path Programs is launching a three-day course targeted at medical professionals (i.e., those experts who would sign FDA Form 1572 before participating in an investigation). Through lectures and discussions, more than 20 FDA senior staff from the Agency's Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), and Center for Devices and Radiological Health (CDRH) will present the scientific data needed to support clinical trial development; the regulatory framework around clinical trials (in terms of ethics, safety, and data integrity), and practicalities in the conduct of trials. This course will be crucial in efforts being made to improve the quality and efficiency of clinical trials. It will provide FDA with an opportunity to reach out to the clinical trial community and to encourage communication with the Agency. Designed for physicians and senior healthcare professionals, the first course is scheduled to begin in November 2009; the course is expected to be offered annually.

[12] Kaitin, K. (editor), Number of Active Investigators in FDA-Regulated Clinical Trials Drop, *Tufts CSDD Impact Report,* Boston, MA., Volume 7, Number 3 (2005), Page 2.

7. Facilitate the development of a clinical trial to resolve safety and efficacy issues related to Drug-eluting stents

Challenge: Concern exists that the dramatic efficacy of drug-eluting stents (DES) in clearing narrowed coronary heart arteries, compared with bare metal stents (BMS), may be offset by stent thrombosis, an uncommon but serious complication associated with myocardial infarction or sudden death. Limited evidence suggests that the risk of late stent thrombosis may be modified by administering aspirin plus thienopyridine, known as dual antiplatlet therapy (DAPT), to patients.

Project: Facilitate the conduct of a DAPT clinical trial by medical product manufacturers and the clinical community to determine the comparative benefits and risks of extended DAPT versus administering aspirin alone to patients who receive DES and bare metal stents.

Nearly 700,000 patients a year are implanted with drug-eluting stents (DES), a treatment that has proven considerably more effective than implantation with bare metal stents (BMS). However, FDA is concerned that DES might lead to higher rates of stent thrombosis, an uncommon but serious adverse event associated with myocardial infarction or sudden death. The consensus among clinical experts is that the risk of stent thrombosis can be reduced by administering DAPT to patients for an extended duration. But the optimal duration of DAPT administration following stent implantation has not been validated by clinical trials conducted on any of the five FDA-approved DESs. Furthermore, although extending the duration of DAPT administration may decrease the risk of very late stent thrombosis, this strategy may also result in an increased risk for major bleeding complications.

FDA's Office of Critical Path Programs is facilitating the design and conduct of a DAPT trial by regulated industry and the clinical community to resolve issues related to this important combination product. The effort will leverage the shared resources of project participants to enable collaborators to find answers to challenges involved in DES treatment faster and at reduced cost. The study is unprecedented in the level of cooperation required between the drug and device industries and the clinical community.

Project Collaborators: Medical product manufacturers and the clinical community (see a list of collaborators in the attachment)

Center for Biologics Evaluation and Research

The Center for Biologics Evaluation and Research (CBER) took the lead on 17 projects receiving CPI funding during 2008.

8. Enhance tools to detect infectious agents in the nation's blood supply

Challenge: The safety and availability of the country's blood supply must constantly be monitored. However, many blood-borne agents are infectious at levels far below the sensitivity limits of currently available screening technologies.

Project: Develop more sensitive blood screening methodologies.

A host of influences, from the increasing globalization of travel and immigration to new infectious agents and the risks of bio-terror make it imperative that we successfully monitor and protect the U.S. blood supply. FDA is working both to correct current deficiencies in methods used to identify infected blood donors and to increase the sensitivity of blood tests aimed at detecting infectious agents like HIV, and *Trypanosoma cruzi*. For example, FDA has optimized a sample preparation method using new reagents specific for enhancing detection sensitivity. This method can be used to determine whether blood donors harbor *Leishmania.* FDA is also developing a parallel approach to capture low amounts of pathogens like HIV and parasitic agents (Malaria, *trypanosomes*) simultaneously from whole blood. The program's expected outcomes are more sensitive assays, providing more rapid and accurate clinical diagnoses while reducing blood donor screening costs; better guidance to industry on developing modern technologies; and more effective FDA policies.

Project Collaborators: FDA; Walter Reed Army Institute for Research, Silver Spring, MD; Department of Defense (DOD), Washington, D.C.; and American Red Cross, Washington, D.C.

9. Protect the nation's blood supply from contamination from emerging, genetically diverse and drug-resistant strains of human immunodeficiency virus (HIV)

Challenge: Existing diagnostic and blood donor screening assays may not be able to detect these novel strains because of genetic diversity.

Project: Develop an HIV variant reference panel for assay standardization and evaluation of approved/investigational HIV assays and lot release testing.

Throughout the world, new, genetically diverse and drug-resistant strains of human immunodeficiency virus (HIV) have emerged through genetic mutation and will likely continue to spread through global travel and migration. Although concentrated largely in

Africa, Asia, and Latin America, these new strains are present in the United States (their presence has jumped to 5% from 0.5% in the past five years). Existing FDA-approved diagnostic and blood donor screening assays may not be able to detect these novel strains because of genetic diversity. As a result, reference materials are urgently needed to standardize and evaluate the performance of new analyses for detecting these strains. FDA is tackling this problem by characterizing emerging variant strains from Cameroon, a useful model for HIV evolution since viral diversity in this country is very high. The multi-year project will give FDA samples of genetically diverse HIV strains that could be used as reference panels representing strains found worldwide. Testing such materials, which contain rare but diagnostically challenging strains, and making the results publicly available will enable manufacturers to use the data to evaluate new tests for FDA approval in a rapid time frame, based on conventional or emerging technologies.

Project Collaborators: FDA; New York University School of Medicine, New York, NY; National Institutes of Health (NIH), Bethesda, MD; and National Institute for Biological Standards and Control (NIBSC), Hertfordshire, England.

10. Facilitate the diagnosis and treatment of neurological diseases

Challenge: Develop treatments for brain diseases like Parkinson's and Alzheimer's.

Project: Facilitate development of treatments using neural stem cells to replace degenerative brain cells.

Neural stem cells isolated from adult, fetal, and embryonic sources hold great promise for treating degenerative brain diseases like Parkinson's and Alzheimer's. FDA is investigating several drugs that use neural stem cells, but little data have been generated so far to show what happens to the neural stem cells following transplantation and what effect cell manufacturing processes have on safety and efficacy (critical for FDA to approve these types of therapies). FDA has a number of goals for this project, including the following.

- Explore whether neural stem cells can be tracked after they are transplanted into mouse brains, using Magnetic Resonance Imaging (MRI).
- Evaluate a possible biomarker that could be used to help predict the fate and function of cells after they are transplanted.
- Determine the effects of early vs. late cell passage and donor age (fetal vs. adult) on the neural stem cells' ability to implant, migrate, and reproduce.
- Perform preliminary transplantation experiments to determine if iron-labeled neural stem cells can be identified by MRI.
- Create new neural stem cell lines that contain indicators to help identify and see engrafted neural stem cells.

Most of these goals will be achieved during the next 12–18 months.

Project Collaborators: FDA: National Institutes of Health (NIH) Mouse Imaging Facility, Bethesda, MD.

11. Facilitate tools to ensure safety of neural stem cell therapies

Challenge: Neural stem cell therapies show promise but it is critical to ensure their safety and efficacy before marketing approval.

Project: Determine whether it is possible to track neural stem cells after transplantation using magnetic resonance imaging (MRI).

FDA is evaluating whether it is possible to track neural stem cells after they are transplanted into mouse brains, using magnetic resonance imaging (MRI). Understanding what happens to transplanted cells is essential to predict the safety and efficacy of neural stem cell therapies. Additionally, the project is evaluating a potential biomarker to help predict the fate and function of cells after they are transplanted. The project is also studying the effects of early vs. late cell passage and donor age (fetal vs. adult) on the neural stem cells' ability to implant, migrate, and reproduce. Preliminary transplantation experiments have been performed and iron-labeled neural stem cells have been visualized in situ by MRI. New neural stem cell lines have been created containing indicators that make identification and visualization of engrafted neural stem cells possible. Immunohistochemistry is now being used to determine what types of cells the neural stem cells differentiate into after engraftment and to confirm that the iron label is still present within live cells. Quantitative methodologies are being used to analyze the effects of growth conditions on the expression of potential biomarkers that could help measure engraftment capability. Most project goals should be achieved during the next 12 to 18 months.

Project Collaborators: FDA; National Institutes of Health (NIH) Mouse Imaging Facility, Bethesda, MD.

12. Facilitate development of vaccine adjuvant therapies

Challenge: The vaccine field is facing a severe shortage of analytical tools to evaluate new adjuvants, many of which harbor components that produce negative side effects.

Project: Develop alternative methods for predicting unacceptable immunological reactions and systemic toxicities associated with new adjuvants and delivery systems.

Human vaccines have been in existence for many years, but only a few adjuvants are licensed for human use. (An *adjuvant* is a substance added to a vaccine to improve the immune response so that less vaccine is required to give protection.) Both licensed vaccines, such as influenza and vaccines against emerging diseases, are combined with an adjuvant. However, the vaccine field is facing a severe shortage of analytical tools to evaluate these complex products—many of which contain components that produce adverse side effects—for early clinical development. Research into adjuvants is complicated because species differences cause variances in the biological activity of these substances, often

making adverse reactions undetectable in animal studies. As a result, developing rapid in-vitro screening trials based on relevant human cells is important to evaluate new adjuvants and to determine parameters that will predict unacceptable toxicities in humans. A two-year FDA project is seeking to develop alternative methods for predicting unacceptable immunological reactions and systemic toxicities associated with new adjuvants and delivery systems. These human detector lines will also provide alternatives to the traditional assays used for identifying bacterial contaminants in vaccine adjuvants, among other biological products. Preliminary results have already been provided to collaborating adjuvant manufacturing groups. Proof-of-concept data were presented at a November 2008 workshop on nanoparticles safety and at a December 2008 workshop co-sponsored by FDA and the National Institute of Allergy and Infectious Diseases (NIAID). The newly developed assays for preclinical evaluation of new adjuvants will be published in peer-reviewed journals, and the standard operating procedures will be shared with vaccine manufacturers. Additionally, after validation, recommendations for use of these newly developed methods for preclinical evaluation of novel adjuvants may be incorporated into updated guidance documents.

Project Collaborators: FDA; National Institute of Allergy and Infectious Disease (NIAID), Bethesda, MD.

13. Support development of new biomarkers for RBC and blood platelets to protect clinical trial participants

Challenge: Evaluating the efficacy of red blood cells (RBC) and platelets after storage can endanger clinical trial participants.

Project: Facilitate the development and approval of new transfusion products using new biotechnology tools.

Concentrated red blood cells and platelets are vital blood components that undergo physiological changes when stored, adversely affecting their function following transfusion into patients. The current *gold standard* for platelet efficacy evaluation involves an expensive, phase 2 clinical trial that can pose some risk to the trial participants. Identifying biomarkers that could serve as preclinical surrogates of red blood cells and platelet efficacy following storage would make it easier to bring safe, new, and effective products to the market. FDA is working to facilitate the development and approval of transfusion products by using advanced approaches in biotechnology to develop red blood cell- and platelet-specific biomarkers to predict clinical efficacy. This project will ultimately help reduce the need for clinical trials as well as improve the quality and supply of platelets and red blood cells, thus benefiting the field of transfusion medicine and public health. Work is anticipated to be completed by autumn 2010.

Project Collaborators: FDA; Dartmouth Medical School, Hanover, New Hampshire.

14. Support the development of blood substitutes

Challenge: Although blood substitutes show great promise, they can produce toxicity in humans.

Project: Develop new animal models and qualify biomarkers to predict and monitor the toxicity of blood substitutes.

Nonclinical evaluations show encouraging evidence that hemoglobin-based oxygen carriers (HBOCs), also known as *blood substitutes*, can deliver oxygen and reduce the need for blood transfusions. HBOCs have many potential advantages over human blood. They are (1) easily available, (2) compatible with all blood types, (3) have a long shelf life, and (4) are free of blood-borne agents. However, to date, clinical trials to test the effectiveness and safety of HBOCs in humans have shown these products can produce significant toxicity. The project's goal is to provide a roadmap for designing and developing safe and effective HBOCs. Specifically, FDA's CBER is working to create improved animal models and biomarkers to better predict and monitor toxicity and ultimately enhance the safety of blood substitutes in humans. Researchers are also creating a database on how different native protein modifications alter the structure, function, and stability of HBOCs. Proper characterization of HBOCs is already becoming predictive of toxicity, and preclinical animal testing is becoming more predictive of the performance of these products in humans. Project results will enable FDA to devise appropriate guidance on product development to support the creation of these blood substitute products.

15. Advance the field of nanotechnology

Challenge: Fullerene and carbon nanotubes seem to be an ideal nanomaterial for a variety of biomedical applications. But their effects on tissues remain unclear.

Project: Identify possible harmful effects of carbon nanomaterials.

Carbon occurs in nature in two well-known forms—graphite and diamond. But less well known forms called carbon fullerenes and nanotubes are key materials used in biomedical nanotechnology. The elasticity and tensile strength of this material makes it ideal for a variety of biomedical applications. But determining the effects of carbon nanomaterials on blood and blood vessels remains a critical safety issue. FDA has been investigating potential harmful effects of carbon nanomaterials on the highly sensitive cells lining the inner surface of blood vessels, known as endothelial cells, and the effects on blood platelets, which play a key role in blood clotting. Both endothelial cells and platelets are major contributors to the development of atherosclerosis and other thrombotic diseases, like heart attack and stroke.

An FDA pilot study, described in the March 2008 issue of *International Journal of Nanomedicine*, showed that fullerenes can kill endothelial cells cultured in a dish by a mechanism of programmed cell death called apoptosis. In a subsequent study, presented in December 2008, the project demonstrated that carbon nanotubes (CNTs) activate blood platelets to promote blood clotting. Given the wide potential applications of fullerenes and CNTs, thoroughly evaluating their possible safety issues is essential. The pilot project results

call for additional in-depth studies to explore harmful effects of carbon nanomaterials on the cardiovascular system in exposed populations. FDA researchers are investigating what structural features of fullerenes and CNTs play key roles in the toxic effects on blood and vasculature. This project will help clarify the structure—toxicity relationship of carbon nanomaterials. This is crucial for evaluating the safety of different types of recently developed carbon nanomaterials. It will also help in designing new carbon nanomaterials with optimal biocompatibility for biomedical use.

Project Collaborators: FDA; Nanotechnology Characterization Laboratory, National Cancer Institute, Bethesda, MD.

16. Facilitate progress in the field of flow cytometry

Challenge: Flow cytometry is widely used in drug development as well as disease detection and progression, but measurements are not reproducible across laboratories in clinical trials.

Project: Standardize test calibrations for flow cytometry to make them reproducible across laboratories during clinical trials.

Flow cytometry (FCM), a technique for counting, examining, and sorting microscopic particles suspended in a stream of fluid, plays a critical role in cell and gene therapy product development and in devising in vitro diagnostics. In cancer, for example, flow cytometry is key in early detection using surrogate biomarkers to define initial events like early incidences of leukemic transformation and in tumor progression. However, to be dependable, flow cytometric measurements are often not reproducible across laboratories during clinical trials, a major gap in developing cancer therapies and diagnostics. FDA is developing quantitative methods for flow cytometry, an approach that enables reproducible measurements of cell populations and their surface biomarkers. This standardizing approach can be used to control the quality of cellular products and to discover biomarkers. For example, in the event of a bioterrorism act, markers of abnormal cells could be used to monitor the state of blood cells in individuals after radiation, chemical, or biological exposure.

The discovery of a biomarker in familial chronic lymphocytic leukemia—the most common form of blood cancer in older adults—has been one important project outcome. The project used flow cytometry to detect small populations of abnormal blood cells, whose presence provides a biomarker long before cancer symptoms develop. This work could lead to earlier detection of disease, resulting in a better prognosis for individuals and families, and to new treatment strategies that can be tested in animal models and later in clinical trials. In collaboration with the National Cancer Institute (NCI), Centers for Disease Control (CDC), and the National Institute of Standards and Technology (NIST) the project is (1) devising a national laboratory of fluorescent standards for use in various applications and (2) developing guidance for operator safety and standards for sorting and clinical use of flow cyotmetric-sorted cells. A paper outlining the project has been published.[13] Together with

[13] Wang L, Gaigalas AK, Marti G, Abbasi F, Hoffman RA. Toward Quantitative Fluorescence Measurements with Multicolored Flow Cytometry. *Cytometry,* Dec 2007, http://www.ncbi.nlm.nih.gov/pubmed/18163471?dopt=Abstract, accessed February 20, 2009.

the Clinical and Laboratory Standards Institute (CLSI), the project is revising current guidelines and investigating a change in the level of CD4 binding reagents. The FDA is collaborating with NIST and NCI to perform the experimental work and complete revision of an earlier guidance.[14]

Project Collaborators: FDA; National Cancer Institute (NCI), Bethesda, MD; Centers for Disease Control and Prevention (CDC), Atlanta, GA; National Institute of Standards and Technology (NIST), Gaithersburg, MD; Clinical and Laboratory Standards Institute (CLSI), Wayne, PA.

17. Validate methods to assess the safety of cellular and gene therapies

Challenge: Innovative new therapies (e.g., cellular and gene therapies) have short shelf lives and require new, automated, and rapid testing for possible bacterial contamination.

Project: Validate new testing technologies by performing a comprehensive comparison with traditional testing methods.

Today, cellular and gene therapy products are being used increasingly to treat medical conditions like cancer, diabetes, and autoimmune diseases. Unlike traditional drugs, which have a relatively long shelf life, these novel therapeutics may last for only hours. Traditional methods for determining whether a drug is sterile typically take 14 days. When these novel products are administered to patients before the test results are confirmed, patients may be at risk for infection. Instruments have been developed for use in hospital laboratories that provide automated read out of sterility test results, and these tools show promise in facilitating more sensitive and rapid detection of possible product contamination. However, a comprehensive comparison of the automated to the traditional methods has not been made. FDA's CBER is coordinating an effort to make existing data on rapid sterility test methods publicly available. As part of the project, existing data are being reviewed to identify gaps and to coordinate and design studies to generate additional data. The studies will be conducted by a collaboration of instrument developers, sponsors representing products of different cell types, and other government agency groups.

[14] NCCLS Document ILA24-P: *Fluorescence Calibration and Quantitative Measurement of Fluorescence Intensity; Approved Guideline Development of Fluorescence Intensity Standards.*

18. Facilitate the development of gene therapies

Challenge: Current approaches for assessing the safety of retroviral vectors are expensive and require lengthy time frames.

Project: Develop new tools to assess retroviral vector safety more efficiently.

Children in two European gene therapy clinical trials for an immunodeficiency disease have developed leukemia after being treated with a retroviral vector gene therapy that activated known human oncogenes. (An oncogene is a gene that has the potential to cause a normal cell to become cancerous.) Researchers are working to develop retroviral vectors with reduced risk of causing cancer. Currently, however, the best method to assess a new retroviral vector's potential to cause cancer depends on a one-year animal study. Methods with shorter time periods would make it easier to screen and develop safer gene therapy agents to treat various conditions, from inherited disorders to cancer. FDA is collaborating with Germany's Hannover Medical School to define optimal parameters and target cells for an in vitro assay method that is reproducible, sensitive, and quantifiable in detecting retroviral agent-mediated cell transformation. The project completion date is set for 2010. Project results will be published in peer-reviewed journals.

Project Collaborators: FDA; Hannover Medical School, Hannover, Germany.

19. Improve our understanding of virus-based cancer treatments

Challenge: Viruses can be used to transport therapies to tumors, but questions remain about safety testing of adenovirus vectors and biological barriers to using adenovirus gene therapies for systemic cancer therapy.

Project: Resolve remaining barriers to virus-based cancer treatments.

Viruses no longer just cause colds. Viruses like adenovirus, which takes its name from the tissue it often infects, can also deliver therapies. Carried by a virus-based vector (i.e., transporter), these therapies make up an innovative class of products that are under intensive investigation as cancer treatments. Currently, more than 80 investigational studies are under way using adenovirus gene therapies.

However, multiple sponsors have repeatedly encountered the same problems with adenovirus vectors, resulting in delays in clinical development and limiting the usefulness of vectors for systemic delivery to metastatic tumors. FDA is taking the lead in a way that individual sponsors cannot to solve these problems. As part of a two-part project, FDA is addressing (1) problems related to safety testing of adenovirus vectors and (2) removing biological barriers to using adenovirus gene therapies for systemic cancer therapy. Results of successfully achieved project milestones were presented in June 2008 to the American Society of Gene Therapy. A manuscript has been published in a peer-reviewed journal that demonstrates how adenovirus vectors are rapidly cleared from the circulation. Ongoing work will examine how to circumvent these barriers.

Project Collaborators: FDA; National Cancer Institute (NCI), Bethesda, MD; University of Washington, Seattle, WA.

20. Improve the quality of allergen extracts in diagnosing and treating allergic disease and asthma

Challenge: Estimating overall potency of unknown allergens may be insensitive to clinically significant changes in individual allergens, causing major alterations in potentially important specific allergens to go undetected using existing assays.

Project: Test the use of the multiplex allergen extract potency assay for its sensitivity to allergen extracts.

Allergen extracts are widely used for diagnosing and treating allergic disease and asthma. Allergen standardization has permitted the assignment of common and accepted units to several allergen extracts, including grass pollens and dust mites. This has enabled researchers to perform studies on these extracts using a common, agreed-upon unit and has also enabled clinicians to administer allergen extracts more reliably and safely. Existing allergen extract potency assays estimate extract strength by one of two methods, depending on whether the specific allergen is known or unknown. When the specific allergen is unknown, overall potency is estimated. However, data have shown that this approach may be insensitive to clinically significant changes in individual allergens. Thus, large fluctuations within an extract of potentially important specific allergens may go undetected. To address this issue, FDA is using a new method called multiplex allergen extract potency assay (MAEPA) to assess simple extracts, such as cat and short ragweed. The next step is to use MAEPA to assess complex extracts like grass pollens, dust mites, molds and German cockroach (German cockroach allergy has been shown to be important in the development of inner city asthma). This will make it easier to use complex extracts like German cockroach allergen extract more safely and effectively for diagnosing and treating allergic diseases and asthma.

Project Collaborators: FDA; University of Virginia, Charlottesville, VA.

21. Reduce the incidence of transfusion-transmitted babesiosis in the United States

Challenge: Cases of transfusion-related transmission of babesiosis infection are increasing.

Project: To reduce the cases of transfusion-related babesiosis infection in the United States.

Babesiosis, a malaria-like illness, is both a naturally occurring and transfusion-induced infection present in some parts of the continental United States. To date, more than 70

cases of the infection have occurred in the country as the result of blood transfusions, and reports of fatal transfusion-transmitted babesiosis have recently surged. Yet, there is neither a licensed laboratory test that can identify donors infected with babesia nor donor deferral guidance based on the risk of exposure to babesia parasites to ensure that patients are safe from transfusion-transmitted infection. FDA has launched an effort to address the serious risk that babesia-infected donors present to the nation's blood supply.

At a September 2008 public workshop, experts in the field discussed the risk of *Babesia* infections through transfusion of blood and blood components; laboratory methods to detect *Babesia* infections; and possible approaches, including donor deferral and donor testing, to reduce the risk of transfusion-transmitted babesiosis. Experts agreed on the need for additional research to develop suitable tests to identify blood donors infected with the parasites. As a result, a task force comprising experts from academia, blood establishments and government agencies has been created to prepare recommendations on how to identify, defer, and re-enter donors with risk of transmitting *Babesia*. FDA is also preparing a report on the workshop findings for publication in a peer-reviewed scientific journal with the goal of disseminating the information and raising awareness about the risk of contracting *babesia* infections through blood transfusion to physicians, blood banking establishments, and the general public.

22. Develop a new trial design for testing vaccine efficacy

Challenge: Vaccine approval is contingent on conduct of and data from a large efficacy trial. Once a vaccine is approved, it is difficult to conduct another large trial for a similar vaccine. However, a small immunogenicity trial can aid in regulatory decision-making if knowledge of the immunogenicity threshold is known. This project aims to estimate the immunogenicity threshold for some vaccines.

Project: Perform a large, multi-year meta-analysis of vaccine safety, efficacy, immunogenicity, and their inter-relationship using data from sponsor submissions to FDA. The ultimate goal is to estimate the immunogenicity threshold for approval of a vaccine when a large efficacy trial is not possible.

When the incidence rate of infection by a vaccine target pathogen is small, the clinical trial design to prove the efficacy of a vaccine requires a large sample size. However, if a licensed vaccine for the same target pathogen already exists, it is unethical to conduct another efficacy trial with a placebo control. If immunogenicity (immune response) can be used as a surrogate for estimating vaccine efficacy, then a much smaller number of subjects will be needed (hundreds instead of thousands). This requires knowledge of the true relationship between immunogenicity and the efficacy of the vaccine. Vaccine sponsors have submitted a large amount of immunogenicity and vaccine efficacy data to FDA, but they are in a variety of formats and are unsuitable for analyzing collectively. FDA's CBER is leading a two-year project to convert submitted data from some regulatory submissions for vaccines to a standardized format (SDTM, an FDA-compliant format) so that meta-analysis can be used to identify relationships between efficacy and immunogenicity. One of the project's objectives is to use data from vaccines against a common target pathogen to find an immunogenicity threshold that can be used to estimate vaccine efficacy for those vaccines. An Oak Ridge Institute for Science and Education (ORISE) fellow was hired in August 2008, and another is

being hired to accelerate the conversion. The database construction is scheduled for completion in December 2009. The project aims to have the meta-analyses completed by June 2010, and results published by the end of 2010.

23. Improve the efficacy of hepatitis C immune globulin products

Challenge: Recurrent hepatitis C in transplant recipients is very difficult to treat and new approaches are urgently needed.

Project: Facilitate approval of HCV-IGIV products.

Chronic hepatitis C virus infection, which can lead to liver cirrhosis and cancer, is now the leading reason for liver transplantation in the United States. Unfortunately, when a healthy liver is transplanted into an individual infected with hepatitis C, the new organ also becomes infected. Since recurrent hepatitis C in transplant recipients is very difficult to treat, new therapeutic approaches are urgently needed. FDA is leading a two-year effort to improve the clinical efficacy of hepatitis C immune globulin products and develop a relevant potency assay for prophylaxis and treatment of HCV infection. Recent FDA studies[15] emphasize the importance of removing antibodies that interfere with efficacy from HCV-IGIV products in development. Research is being conducted on how to deplete interfering antibodies from currently available HCV-IGIV products, improving these products and facilitating their licensure. During year two of the project, the research goal is to validate the potency assay according to FDA and ICH[16] guidelines. As the project develops and provides meaningful and consistent results, relevant information will be discussed with stakeholders, including manufacturers, at appropriate forums (e.g., advisory committee meetings).

Project Collaborators: FDA; Department of Transfusion Medicine, Warren Grant Magnuson Clinical Center, National Institutes of Health (NIH), Bethesda, MD.

[15] Zhang et al. Hepatitis C virus epitope-specific neutralizing antibodies in Igs prepared from human plasma. *PNAS* 104, 8449-8454, 2007.
[16] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

24. Create new tools and methods to enable analysis and management of different types of data

Challenge: Recent developments in bioinformatics, including the launch of FDA's Sentinel Initiative (see project #1), hold the promise of transforming the way we monitor the safety and efficacy of medical products through the use of large data sources. But to make this type of querying and data mining possible, we need to create new tools and methods to enable the analysis and management of different types of data.

Project: Start analyzing one of four databases for usefulness in assessing vaccines, tissues, blood, and allergenic products and evaluate data accessibility, quality, data mining, as well as new and traditional epidemiological methods to determine the best data sources and practices for the range of products, populations, and issues that arise with biologic products.

Medical product safety and effectiveness under real-world conditions can be assessed more rapidly thanks to recent advances in bioinformatics that facilitate data mining and analysis using large databases. FDA is collaborating with others to develop new tools to monitor the safety and effectiveness of biological products using large public and private healthcare databases. This study has been launched to (1) start evaluating one of four databases for usefulness in assessing vaccines, tissues, blood, and allergenic products and (2) evaluate data accessibility, quality, data mining, and new and traditional epidemiological methods to determine best data sources and practices for the range of products, populations, and issues that occur with biologic products. This project will also help build the interagency collaboration and interdisciplinary staff necessary to use these types of databases effectively to support FDA's regulatory mission. In September 2008, FDA awarded contracts to expand access to databases for assessing biologic product safety. During the next few years, FDA will assess these new data sources for vaccine, blood, and tissue safety. This project will directly inform FDA's Sentinel Initiative.

Project Collaborators: FDA; HMO Research Network (HMORN) (NCI). Bethesda, MD; Kaiser Permanente, Bethesda, MD; Surveillance Data, Inc.(SDI), Plymouth Meeting, PA; HealthCore, Wilmington, DE; and i3Drug Safety, Basking Ridge, NJ.

Center for Drug Evaluation and Research

The Center for Drug Evaluation and Research (CDER) took the lead on 13 projects receiving CPI funding during 2008.

25. Personalize cancer treatment through biomarker development

Challenge: Tumor-resistance to cancer therapies is one of the main causes of failure in treating cancer. The ability to predict an individual patient's response to a cancer therapy will make developing cancer therapies safer and more effective.

Project: Identify biomarkers to predict tumor responsiveness to a promising new class of biologic products, known as death receptor-targeting therapies, for effective treatment of cancer.

FDA scientists at Agency centers CDER and CBER are working to identify genes (pharmacogenomic biomarkers) that could predict how a cancer patient would respond to this new class of cancer therapies. This project has established three milestones to be achieved in the first year and one in the second. A report on the project's findings has been published in *Molecular Cancer Research,* and several experiments are under way to identify biomarkers that predict tumor response to treatment with death receptor-targeting therapies.

Collaborators: FDA centers

26. Assess PET imaging for use with cancer treatments

New, noninvasive imaging techniques like PET[17] scans show tremendous promise for individualizing cancer treatments. FDA scientists are evaluating the potential of PET imaging to rapidly predict whether a specific tumor will respond to a certain drug, without exposing the patient to the drug's life-threatening toxicity levels. First, the anti-cancer drug docetaxel will be radiosynthesized. Next, PET imagining will be used to track the movement and accumulation of radioactive docetaxel in rodent tissue. Finally, in collaboration with the National Cancer Institute, radioactive docetaxel will be administered to and accumulation tracked in cancer patients. The study will establish the ability of PET imaging to classify a patient's tumor as sensitive or resistant to drug treatment and will increase understanding of drug resistance and drug delivery issues.

Collaborators: FDA; 3D Imaging, Maumell, AZ; NIH's National Cancer Institute.

[17] PET stands for positron emission tomography, an imaging technique that provides a picture of where in the body a positron-labeled compound accumulates.

27. Develop New tool to analyze the effects of drugs on the heart

Challenge: The vast number of electrocardiograms (ECGs) submitted annually provide FDA with a wealth of clinical trial data that could yield vital information about the effects of drug products on the heart. However, concerns about exposure of proprietary or personal information remain.

Project: Develop and implement a portal through which investigators can obtain summary of statistical data from ECGs even if the investigators do not have permission to view individual ECGs.

FDA has been working with Mortara, Inc. to develop an electronic repository to hold electrocardiograms (ECGs) submitted to FDA as part of medical product marketing applications. That repository now holds more than 3 million ECGs from more than 300 clinical studies. FDA is working to develop tools that will enable researchers to evaluate repository ECGS for the effects of drugs on the heart's electrical properties while protecting proprietary information. Major project milestones include completing the development of a database and interface tools by early 2009, which will enable extensive data mining. A pilot project is under way to test the database and interface tools. The team hopes to make publicly available a description of the system architecture that can serve as a model for providing protected access to other kinds of clinical trial data such as pharmacogenomic data.

Project Collaborators: FDA; Mortara, Inc., Milwaukee, WI.

28. Facilitate efficient development of analgesic drugs

Challenge: Available analgesic drugs to treat acute and chronic pain can be toxic, limiting their usefulness. Although urgently needed, efforts to develop new treatments frequently fail during clinical trials because of toxicity.

Project: Mine data from past clinical trials for analgesics and create new trial designs to speed the creation of safer and more effective analgesics.

The many new analgesic drug applications submitted for approval during the last decade are a rich information source that can be analyzed for ways to reduce failure in clinical trials. FDA is evaluating these data to create new clinical trial designs that can help expedite development programs for more effective and less toxic painkillers. FDA is training experts on how to examine the data in a new drug application and extract information relevant to the project. These experts would be under contract agreements that allow them to access proprietary information. A number of contracts have been issued to transform and standardize the datasets to enable efficient analysis. The goal is to publish a series of articles in peer-reviewed medical journals documenting the research findings and recommendations for better pain medication trials and development programs. This

knowledge base will serve as a scientific foundation for new drug development programs for analgesics.

Project Collaborators: FDA; University of Pennsylvania, Philadelphia, PA; University of Pittsburgh, Pittsburg, PA; and SAS Institute, Cary, NC.

29. Improve quality and efficiency of commonly used inhalation products

Challenge: The incidences of asthma and chronic obstructive pulmonary disease (COPD) are increasing. More efficient, more user-friendly, and cheaper treatment options are needed.

Project: Since the summer of 2008, FDA has been working to develop new methods and standards for characterizing inhalation products used to treat asthma and chronic obstructive pulmonary disease.

COPD is the fourth leading cause of death and the second leading cause of disability in the United States.)[18] Treating these two conditions costs about $62 billion annually.[19] FDA is researching new methods and standards for characterizing inhalation products used to treat asthma and COPD. These improvements are needed not only to ensure product performance but to provide for future generics that will keep healthcare costs down. Inhalation products are also being considered to deliver a variety of other pharmaceuticals, such as migraine medication and insulin. Project results are expected to be published in research journals in 2009. The findings will inform FDA guidance development on bioequivalence of inhalation products.

Project Collaborators: FDA; Washington University, St. Louis, MO.

30. Develop new tools to improve manufacturing quality

Challenge: Drug manufacturing problems can endanger public health and result in severe loss of resources.

Project: Develop a science-based approach to modernizing drug manufacturing.

Manufacturing represents nearly 36% of the pharmaceutical industry's operational costs, and manufacturing problems can quickly turn into safety problems, resulting in harm to patients and lost resources. In 2007, for example, manufacturers recalled 136 over-the-counter drugs and 851 prescription drugs for reasons ranging from incorrect storage (e.g.,

[18] See http://www.nhlbi.nih.gov/health/public/lung/copd/campaign-materials/pub/speakers-guide-with-pp-inserted.pdf.

[19] http://www.lungusa.org/atf/cf/%7B7A8D42C2-FCCA-4604-8ADE-7F5D5E762256%7D/ldd_copd_t4.gif

at improper temperatures) to chemical contamination and label mix-ups.[20] Building efficiency and quality into the manufacturing process from the outset can improve drug safety and could save an estimated $90 billion worldwide.[21] To reduce manufacturing expenditures while improving drug quality, FDA is urging industry to embrace the Quality by Design (QbD) approach for pharmaceuticals. This approach is used today in a variety of other manufacturing sectors, including the airline industry. QbD is a science-based, systematic approach to product and process design, development, and manufacturing that encourages continuous improvement throughout a product's life cycle. In this approach, a multi-dimensional *design space* (or set of identified parameters and expectations) is defined. If a process operates within this design space, it can be expected to produce quality products. FDA is working to develop a science-based method for defining design space that is scale and equipment independent. Studies are under way at FDA's laboratory, and trials at an outside facility are set for early 2009. FDA hopes to share discoveries with industry through publication in a peer-reviewed journal.

Project Collaborators: FDA**;** the National Institute for Pharmaceutical Technology and Education, West Lafayette, IN.

31. Address concerns about membrane transporters during drug development

Challenge: Proteins called *membrane transporters* play a vital role in drug response, but can also cause toxicity.

Project: Develop guidance to address issues related to membrane transporters.

Researchers are gaining an increasing understanding of the vital role membrane transporters (proteins that facilitate the movement of substances across cell and organ membranes) play in the body's response to some therapies. Transporters can facilitate drug response, but also contribute to drug–drug interactions and toxicity. Evidence of a transporter causing toxicity was identified with the antiviral drug cidofovir, used in treating HIV. Transporters can carry cidofovir across membranes into kidney tissue, causing kidney poisoning. Scientists have discovered that this movement can be prevented by administering probenecid along with cidofovir. Co-administration of probenecid is now recommended on the cidofovir label.

As part of a large effort to address concerns related to drug transporters, drug transporter experts, including pharmaceutical scientists in academia, industry, and FDA have joined the International Transporter Consortium, which sponsored a two-day workshop, *Membrane transporters in drug development,* on October 2–3, 2008. Conclusions from the workshop will form the basis of a white paper expected to be published in 2009. This paper will provide a foundation for FDA guidance on what transporter issues to consider when developing drugs.

Project Collaborators: FDA; Drug Information Association, Horsham, PA; University of California, San Francisco, CA.

[20] See: http://www.fda.gov/cder/reports/rtn/2007/14_recalls.htm#number
[21] http://www.pharmafocusasia.com/manufacturing/lean_sixsigma_manufacturing.htm

32. Develop pharmacogenomic tools to address adverse side effects early in drug development

Challenge: Development and approval of candidate drugs is sometimes unnecessarily delayed or halted due to the occurrence of phospholipidosis, a side effect with potential serious toxicity.

Project: Develop pharmacogenomic and metabonomic tools to help distinguish between a harmless side effect and one with potential for toxicity to reduce delays in drug development and approval.

Phospholipidosis is a lipid storage disorder in which excess phospholipids accumulate within cells, an adverse reaction with some drugs. Drug-induced phospholipidosis (DIPL) has been identified as a common side effect in more than 180 marketed and investigational drugs in experimental studies. FDA considers the condition to be a serious adverse reaction. Phospholipid accumulation is associated with several serious genetic disorders that cannot be easily monitored in the clinic. FDA is working on a project that involves genomic analysis of target tissues and investigation of the sensitivity and specificity of lipid biomarkers that can predict phospholipidosis. The research should result in reducing delays in drug development and regulatory approval. The final outcome of the three-year project will be a draft guidance for industry and reviewers that clarifies FDA's recommendations on how to proceed with drug development should DIPL be observed and advises FDA reviewers on how to evaluate a finding of DIPL in a preclinical regulatory study.

Project Collaborators: FDA; Affymetrix, Santa Clara, CA; Nextcea, Woburn, MA.

33. Use QbD to facilitate moving from pilot-scale to commercial-scale pharmaceutical manufacturing

Challenge: Outdated pharmaceutical manufacturing systems affect the quality of pharmaceutical products, slow their time to market, and increase costs due to inefficiencies and extensive regulatory oversight. Especially challenging in pharmaceutical manufacturing is moving from pilot-scale to commercial-scale production.

Project: Develop a scientifically based tool to help translate from pilot-scale to commercial-scale pharmaceutical production.

Efficient and consistent pharmaceutical manufacturing depends on building quality into the process, using the Quality by Design (QbD) approach. In this approach, decisions about commercial-scale design space are made in the laboratory using pilot-scale models. One of the major hurdles researchers face is determining how to translate small-scale results to commercial-scale manufacturing. This project aims to show how systematic experimentation and mechanistic principles (i.e., *transformation analysis*) can be applied to create a manufacturing design space that is scale and equipment independent. Once the design space is determined, minimal verification is required at commercial scale, which reduces the time it takes to bring a product to market. Moreover, knowledge gleaned during transformation analysis can be used during process control of the unit operation. This project also has educational and training dimensions based on the experimental and data collection aspects of the research. The results will be broadly disseminated. Since project launch in 2008, a model system (fluid bed granulation) that demonstrates this concept has been chosen; transformation analysis has been performed; screening experiments have been carried out in FDA's laboratory; and scale-up experiments have been planned at an external contract manufacturing site.

Collaborators: FDA; Leon Levine and Associates, Inc., Albuquerque, NM; Pharmaceutics Internationals Inc (PII) Hunt Valley, MD.

34. Identify and evaluate pharmacogenetic tests for use with specific drugs

Challenge: Genetic variations in patients can cause patients to respond differently to the same drug (e.g., warfarin, which must be dosed very carefully in each individual). Pharmacogenetic tests, used prior to treatment, could help provide vital feedback on an individual, making treatment safer and more effective for that individual.

Project: Evaluate the usefulness of pharmacogenetic testing in making therapies safer and more effective for individual patients and evaluate a prescription-driven feedback program for its ability to speed the use of pharmacogenetic tests in clinical practice.

Pharmacogenetic tests can identify genetic characteristics of individual patients that may affect their treatment. FDA is collaborating with Medco Health Solutions, Inc., whose access to a large patient database will enable FDA to (1) determine the usefulness of

pharmacogenetic testing in making therapies safer and more effective for individual patients and (2) evaluate the value of a prescription-driven feedback program to speed the use of pharmacogenetic tests in clinical practice. Upon receiving a prescription, our collaborator will let patients and prescribers know that the pharmacogenetic test is available, facilitate the testing process and provide pertinent feedback to patients and doctors on the test results. The project's first phase consists of a pilot study with warfarin, conducted to measure the impact of genetic testing for CYP2C9 (the enzyme that clears warfarin from the body) and VKORC1 (a protein that influences the sensitivity of patients to warfarin). In the second phase, research will expand to screen a list of other drug–test pairs (e.g. atomoxetine, tamoxifen, and selected opioids). Efficacy and/or safety will then be compared between the cohort of patients with individualized treatment and the cohort with standard treatment. Results will be published in peer-reviewed literature.

Project Collaborators: FDA centers and Medco Health Solutions, Inc., Franklin Lakes, NJ.

35. Investigate molecular mechanisms contributing to drug resistance in an aggressive form of breast cancer

Challenge: The antibody Herceptin has been successful in treating many cases of an aggressive form of breast cancer known as Human Epidermal growth factor Receptor 2 (HER2+). However, for reasons that remain elusive, some patients are resistant to Herceptin therapy.

Project: Investigate the molecular mechanisms that underlie therapeutic resistance in some breast cancer patients to Herceptin and identify biomarkers that predict resistance to the treatment.

Some 25% of breast cancer patients have HER2+ tumors, which grow and spread more rapidly than other types of tumors. Although the drug Herceptin significantly improves the chances of survival for women with HER2+ breast cancer, some breast cancers that initially respond to this therapy return within a year. This project aims to investigate the molecular mechanisms that contribute to therapeutic resistance to Herceptin and to identify new predictive biomarkers that are involved in resistance to treatment. This three-year project will initially develop an in vitro model of Herceptin resistance cell lines and characterize these cell lines to obtain a better understanding of the molecular mechanisms contributing to resistance to treatment. In year three, a paper describing the findings during the second year will be published and the project will focus on identifying potential biomarkers and developing bioassays that could predict Herceptin resistance to human breast cancer cells.

Collaborators: FDA; Genentech, San Francisco, CA.

36. Develop assays for monitoring immune function during diabetes therapy

Challenge: Dipeptidyl-peptidase (DPP4) inhibitors offer a promising new therapy for controlling glucose levels in Type 2 diabetes mellitus. But pre-clinical studies have also shown that DPPR inhibitors may have a negative effect on immune function and cause upper respiratory infections.

Project: Develop blood assays to study the effects of DPP4 protein inhibitors in vitro and in samples from patients undergoing DPPR inhibitor therapy. This study could provide new surrogate markers to monitor immune function during diabetes therapy.

DPP4 inhibitors effectively control glucose levels in Type 2 diabetes by raising the levels of gastrointestinal hormones, known as GIP and GLP, leading to increased insulin production and secretion. However, there is a downside to DPP4 inhibition because the enzyme DPP4 also plays a key role in the immune system. Specifically, DPP4 controls cell migration by modifying proteins called chemokines that are secreted by cells. Some chemokines serve an important function in immune response by sending cells of the immune system to an infection site. Other chemokines control the migration of cells during normal tissue maintenance and development. Additionally, DPP4 regulates the activity of Neuropeptide Y (NPY), a powerful peptide that can seriously constrict the blood vessels. This project is working to develop new assays to measure the amounts of chemokines and Neuropeptide Y in the blood. The assays will then be used to examine the effects of inhibitors of DPPR proteins in vitro and in samples from patients on DPPR inhibitor therapy. The study could provide new markers to help monitor immune function during diabetes treatment. Moreover, chemokine blood assays can also serve as new tools to monitor immune and anti-viral therapies.

37. Advance personalized therapy using databases in different therapeutic areas

Challenge: FDA's knowledge management tool DMerge will be used to develop large-scale disease databases. Analysis of the information in these databases can help identify approaches to personalizing treatment in individuals with specific diseases. However, hurdles remain in building cross-disciplinary, large-scale databases. A variety of tools will be needed to overcome data format incompatibilities and to analyze the disease databases.

Project: Augment DMerge's capabilities to manage a wider variety of disease data from different therapeutic areas and address efficiency, usability, and compatibility issues.

Disease databases are vital to understanding the progression of a disease, identify predictors of disease risk, determine the influence of genetics on drug response in patients, verify mechanisms of drug actions, and simulate clinical trials. FDA has developed a knowledge management tool called DMerge that can combine large-scale efficacy, safety, pharmacokinetic, pharmacogenomic, demographic, laboratory, and other clinical trial data for quantitative analysis. Dmerge will be critical in developing large-scale disease databases. Although the current version of DMerge has many powerful functions, it needs to be enhanced to handle a wider variety of disease data from different therapeutic areas and to overcome efficiency, usability, and compatibility differences. FDA is enhancing DMerge to achieve efficiency, flexibility, and user accessibility. Key milestones include developing new modules aligned with disease database needs and research objectives in two selected therapeutic areas; completion of at least two development cycles of improvement and implementation for each area; and provision of training to a larger user group.

Center for Devices and Radiological Health

The Center for Devices and Radiological Health (CDRH) took the lead on 12 projects receiving CPI funding during 2008.

38. Improve neurotoxicity testing to make clinical trials safer

Challenge: Evaluating medical devices that come in contact with neural tissue poses unique challenges because of the complexity of the nervous system. How much neurotoxicity testing is needed before introducing an embolization device into a human patient?

Project: Develop a universal CDRH regulatory strategy for neurotoxicity testing of new materials to be used in neurological devices that come in contact with cerebral spinal fluid and neural tissues.

Neurological embolization devices are used to treat cerebral aneurysms and belong to a category of devices that has been difficult to review because of a lack of consensus among FDA, the medical device industry, professional societies, and the public on the appropriate amount of neurotoxicity testing necessary to start clinical studies of embolization devices or allow their marketing (510(k)) or approval (PMA, HDE, PDP). FDA is working toward developing a regulatory strategy for determining the appropriate amount of neurotoxicity testing for new materials used in neurological devices that come in contact with cerebral spinal fluid and neural tissues. To date, a postdoctoral research fellow has been hired and research is continuing on determining the applicability of current neurotoxicity testing standards. A workshop cosponsored by ASTM is slated for May 19, 2009, which should help FDA develop the proposed regulatory strategy for neurotoxicity testing and will support development of guidance for review staff and industry. The workshop will include the medical device industry, academia and FDA.

Project Collaborators: FDA centers CBER, CDER, and CDRH.

39. Develop engineering and imaging design methods for medical device development

Challenge: Modern design methods that could make device development safer and more effective are not being applied to device development.

Project: Apply simulation-based engineering and imaging technologies to device development.

Computer simulation methods used in the automotive and other safety-critical industries urgently need to be adapted to the development of medical devices. These technologies would enable device designers to experience failure without consequences and learn from their mistakes. Progress in this arena is vital for improving products, shortening time to market, and reducing development costs. However, the complexity of living systems and insufficient industry and government support of the necessary programs has hindered development of such tools. FDA is collaborating with relevant stakeholders to leverage simulation-based engineering and medical imaging technologies for use in the medical device industry. The project has a three-fold purpose, to: (1) document best practices related to modeling the cardiovascular system and predicting safety and efficacy of cardiovascular devices; (2) review best practices in simulation-based engineering sciences; and (3) establish a strategy for promoting the development, application, and validation of computational methods for cardiovascular device design and evaluation. To date, workshops have been conducted,[22] staff training materials created, and staff trained. Guidance on computational modeling for cardiovascular devices is being developed.

Project Collaborators: FDA; Stanford University, Stanford, CA; National Heart, Lung, and Blood Institute, Bethesda, MD; The National Science Foundation, Arlington, VA; and Massachusetts Institute of Technology, Cambridge, MA.

[22] (http://www.fda.gov/cdrh/meetings/031808workshop)

40. Develop new tools to identify risk of treatment-related kidney damage

Challenge: Current tests are not sensitive enough to pick up clinically significant kidney injury.

Project: Identify safety biomarkers of kidney injury to improve public health and facilitate creation of new disease therapies.

Acute kidney injury affects about 5% of patients in the hospital and about 30% of patients in the intensive care unit. Patients in the hospital can develop acute kidney injury after being treated with certain drugs (e.g., aminoglycoside antibiotics) or after undergoing procedures with certain medical devices (e.g., cardiopulmonary bypass). Kidney damage is typically assessed in the hospital or doctor's office using two common blood tests, both of which are insufficiently sensitive. A patient can lose almost half of his or her kidney function before changes can be detected using current blood tests! Because detecting even subtle kidney injury early is essential for clinicians to implement renal protective strategies, identifying more sensitive biomarkers of altered renal function is crucial. To date, the project has evaluated a suite of new biomarkers to identify kidney damage. The most promising of these is being used to address questions of regulatory significance to the Agency. For example, we are using the biomarkers to assess kidney damage in patients undergoing cardiopulmonary bypass, in rats following ingestion of the food contaminant melamine, and in rats after exposing their kidneys to diagnostic ultrasound. Two peer-reviewed papers were published on this work in 2008 and several manuscripts are being prepared that will be submitted to peer-reviewed journals, describing the successful identification of a number of safety biomarkers of acute kidney injury.

Project Collaborators: FDA; Harvard Medical School, Cambridge, MA.

41. Developing an imaging biomarker that can be used to study ablation treatments for breast cancer

Challenge: A variety of devices can successfully destroy, by burning or freezing (e.g., through thermal ablation), small cancers of the breast, but lack of a validated imaging tool to follow ablated cancers left in-situ has prevented scientists from furthering research in this area.

Project: To correlate imaging as a biomarker for pathology for thermally ablated cancer tissue.

Thermal ablation devices, which kill cells through freezing or heat, are being studied as a local treatment for tumors. Feasibility studies of thermal ablation devices for the treatment of breast cancers, which generally consist of tumor ablation followed by resection with pathologic assessment, have used cryoablation, radiofrequency ablation, focused ultrasound, interstitial laser, and microwave devices. Some investigators have reported nearly 100 percent ablation accuracy. However, the lack of uniformity among different feasibility study protocols has resulted in study findings that cannot be easily compared. This makes it difficult to correlate imaging with pathology and to develop "best practices" for breast cancer thermal ablation.

To resolve this problem, FDA is working to stimulate the development of feasibility studies with a common framework. Such a protocol might be useful for validating the correlation between imaging and pathological results, and it might speed the transition to longitudinal studies of operative resection versus thermal ablation.

Project Collaborators: FDA; National Cancer Institute, Bethesda, MD.

42. Reduce the risk of heart failure during clinical trials

Challenge: Heart failure occurs when the heart can't pump enough blood to satisfy the needs of the body.

Project: Develop biomarkers for evaluating device interventions to facilitate recovery from heart failure.

Heart failure is a chronic condition that affects 1.5% of the American public and is the leading cause of hospitalization of the elderly. An FDA project is underway to develop biomarkers for evaluating device interventions for recovery from heart failure during clinical trials. This project should help in the development of better markers to evaluate heart failure and recovery in other situations as well. In this project, the marker takes advantage of a magneto-hydrodynamic (MHD) signal that is seen on an electrocardiogram (ECG) when a patient is in an MRI magnet. The signal components help track blood flow magnitude, direction, and location. The information contained in the signal is supplementing present-day, non-invasive blood-flow measurements for assessing heart failure. Four of six milestones have already been met, and the project's completion date is set for 2010. A

guidance document recommending a uniform set of MHD-based biomarkers for assessing heart failure recovery will be produced to assist drug developers using this new tool.

Project Collaborators: FDA; Uniformed Services University for the Health Sciences, Division of Cardiology, Bethesda, MD; Foundation for Research on Information Technologies in Society (IT'IS), Zurich, Switzerland; Schmid & Partner Engineering AG, Zurich, Switzerland; University of Florida, Gainesville, FL.

43. Develop standardized techniques for assessing computational fluid dynamic methods in medical device development

Challenge: Currently, no standardized techniques exist for evaluating computational methods in the development and safety assessment of new medical devices.

Project: Increase the use of validated computational simulations in evaluating medical devices. Develop standards for assessing benefits and risks.

Computational fluid dynamic (CFD) methods for describing flow patterns and fluid forces are increasingly being used during the development as well as premarket and postmarket evaluations of blood-contacting medical devices like prosthetic heart valves. Although computer simulations can decrease the need for expensive testing, their usefulness to FDA and industry in analyzing the safety of medical products is limited because reliable standardized techniques for assessing the validity and limitations of CFD simulations and their predictions for blood damage do not exist. FDA is exploring ways to increase the capability of computational simulations in evaluating medical devices. FDA, academia, and industry began collaborating on the project in 2007 with the goal of creating computational and physical models of medical devices that could be evaluated jointly and the results compared. The effort will result in (1) better techniques for using computational simulations to predict flow patterns and blood damage (FY 2010); (2) FDA guidance on using CFD that should help expedite device marketing applications to FDA (FY 2009 and 2010); and (3) an FDA Website[23] that will include a results database that can be used in developing new medical devices.

Project Collaborators: FDA; Mississippi State University, Starkville, MI; Pennsylvania State University, University Park, PA; and Rochester Institute of Technology, Rochester, NY.

[23] www.fda.gov/cdrh/cfd/index.html

44. Develop regulatory pathway for nanotechnology

Challenge: Gaps in our understanding of the safety and effectiveness of nanomediated devices and drugs based on nanoscale components create major hurdles to the use of this technology in developing medical therapies.

Project: Develop a regulatory pathway for nanotechnologies.

FDA is working to facilitate the development, evaluation, and approval of devices and drugs that use nanotechnology. The Agency understands the need to creating a regulatory pathway supported by best practices and guidance for industry and reviewers on developing nanomediated medical products. New tools are needed to:

- Develop methodologies and standards to evaluate the safety and efficacy of nano-based drugs and devices
- Educate industry and FDA experts on best practices for nano-based drug and device development
- Translate nanotechnology research outcomes into public-health applications

FDA has taken the lead in a broad nano-related project. The project is emphasizing methods development, product review, tracking nanotechnology submissions for pre- and postmarket surveillance, and drafting specific guidelines for evaluating nanotechnology devices to ensure efficient product development and a consistent, timely device approval process. Nanotechnology product-tracking and database management efforts that serve reviewers and postmarket monitors have already been started. FDA has developed and put in place a reviewer network, and is sponsoring seminars for industry and academia to broaden the knowledge base.

Project Collaborators: University of Maryland, College Park, MD; George Washington University, Washington, D.C.; University of Florida, Gainesville, FL; University of Maryland, College Park, MD; National Institute of Science and Technology (NIST), Gaithersburg, MD; and National Cancer Institute (NCI), Bethesda, MD; Thomas Jefferson University, Philadelphia, PA.

45. Improve treatments for diabetes

Challenge: It is difficult for people with diabetes to maintain blood glucose levels within the normal range.

Project: Develop an artificial pancreas that will automatically regulate blood glucose levels.

During the last 20 years, the number of people with diabetes worldwide has skyrocketed from 30 million to 230 million—by 2025, the number could reach 350 million. Diabetes accounted for the second highest growth in prescription drug spending in 2006, second only

to cholesterol drugs.[24] But the health prospects of millions of diabetics may soon brighten. FDA researchers are collaborating with stakeholders ranging from patient groups and academic researchers to product developers, industry, and other government groups to expedite and optimize R&D efforts in this area. Efforts are focused on an artificial pancreas that could maintain blood glucose levels within normal ranges through mechanical or bio-mechanical means with little to no patient involvement. This is something that most diabetics are unable to do, even with intensive therapy. This medical breakthrough could dramatically reduce or eliminate the disease's devastating consequences, including blindness, kidney failure, neuropathy, cardiovascular disease, and death. A public workshop in July 2008 highlighted the areas hampering development of the artificial pancreas and discussed possible solutions. FDA is developing guidance for product developers to help expedite development and approval.

Project Collaborators: FDA; Juvenile Diabetes Association, Harrisburg, PA; the National Institute of Digestive Disorders and Kidney (NIDDK), Bethesda, MD; National Institute of Child Health and Human Development (NICHD) Bethesda, MD; National Institute of Biomedical Imaging and Bioengineering (NIBIB), Bethesda, MD; Juvenile Diabetes Research Foundation (JDRF) New York, NY; Diabetes Technology Society (DTS), Foster City, CA; and Children With Diabetes, Superior, CO.

[24] International Diabetes Federation and Medco Health Solutions' 2007 Drug Trend Report

46. Improve intrapartum fetal monitoring

Challenge: Fetal monitoring during labor could be dramatically improved by employing electronic monitors with computer-assisted diagnostic (CAD) features. These computer-assisted devices could be used during labor to help clinicians focus on suspicious monitoring trends by providing periodic warnings and ruling out signal patterns of minimal concern.

Project: Facilitate development of computer-assisted devices to aid fetal monitoring during labor.

FDA believes a new paradigm is needed to stimulate innovation in the development of fetal monitoring devices. Electronic monitors with computer-assisted diagnostic (CAD) features to be used during labor could potentially help clinicians focus on suspicious monitoring trends by providing periodic warnings and by ruling out signal patterns of minimal clinical concern. FDA collaborated with the National Institute of Child Health and Human Development (NICHD), the obstetrics academic clinical community, and industry in planning a meeting on issues concerning evaluating intrapartum monitors with CAD features. The purpose of the November 10, 2008, workshop *Intrapartum Electronic Fetal Monitoring (EFM) with computer-assisted diagnosis (CAD): Exploring Methods of Evaluation* was to gather ideas on current technology and to investigate the different methods for evaluating CAD effectiveness. The FDA/NIH collaboration also produced a white paper providing a brief background on fetal monitoring and some potential assessment paradigms; study designs that may be useful for evaluating the diagnostic performance and clinical value of these devices. The project's next step is to assess the feasibility and value of a guidance document for developers of various forms of this technology. Contingent upon an in-house consensus, a guidance document will be produced to assist developers as they evaluate and create modern fetal diagnostic devices. The timeframe for these steps is 2009–2010.

Project Collaborators: FDA; National Institute of Child Health and Human Development (NICHD), Bethesda, MD.

47. Software for Bayesian driven clinical trials

Challenge: Currently, the software tools that are needed for designing and analyzing Bayesian (a statistical theory useful in the solution of theoretical and applied problems in science) clinical trials are not available in any validated, commercially viable, easy-to-use software package. Consequently, statistical analyses for these trials must rely on custom-written programs that are time-consuming to write and debug.

Project: Develop validated Bayesian software that can be used by FDA statisticians when analyzing marketing submissions to the Agency.

Using Bayesian studies during FDA application review could help shorten time to market for certain medical products. FDA is planning to co-develop software with a large statistical software company under a CRADA. [25] The software development is being carried out in phases, with Phase 2, beta testing set for completion by the end of fiscal year 2009. The project will result in a commercially viable product that can be used by FDA and industry statisticians to design and analyze Bayesian clinical trials.

48. Qualify CT imaging for use in early detection of lung cancer

Challenge: Computed tomography (CT) imaging, also known as *CAT* scanning (computerized axial tomography), is used for diagnostic and treatment purposes. However, because the technique for reading these images is not standardized (i.e. the settings are different), it is not possible to get a comparable image every time a scan is taken. Nonstandardization limits the use of imaging-based measures as surrogate endpoints (the image is a surrogate endpoint) of the response to a drug in clinical trials of new lung cancer treatment.

Project: Improve procedures for early detection of lung cancer and its response to therapy.

Computed tomography (CT) imaging, also known as CAT scanning (computerized axial tomography), produces cross-sectional images or *slices* of anatomy that can be used for diagnostic and therapeutic purposes. FDA is collaborating with the National Cancer Institute (NCI) and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) to improve procedures for detecting lung cancer and patients' early response to therapy. The project goal is to evaluate procedures that will maximize the use of CT imaging for lung cancer and tumor therapy evaluation. Project results have already appeared in several peer-reviewed publications and presentations. In December 2008, the project released thousands of CT images to facilitate the benchmarking of image analysis tools. These scans will make

[25] The acronym CRADA, which stands for FDA Cooperative Research and Development Agreement, is an agreement between one or more FDA laboratories and one or more non-Federal parties under which the FDA laboratory provides personnel, services, facilities, equipment, or other resources toward the conduct of specified research or development efforts.

it possible to compare the accuracy and precision of tumor volume estimates from image analysis algorithms and determine the impact of various CT imaging parameters on lesion size estimates. The results will be an important step toward qualifying new volumetric image analysis methods for analyzing response to therapy using auxiliary imaging endpoints. They will also give us vital information on the imaging parameters that require standardization or calibration during CT image acquisition. Findings from the two-year investigation, ending in 2009, will be used to work with developers of image acquisition systems to develop standard imaging protocols for calibrating relevant imaging routines. Guidance on techniques that sponsors should employ when designing and analyzing clinical trials that use imaging as a biomarker should be available during 2009.

Project Collaborators: FDA; The National Cancer Institute (NCI), Bethesda, MD; the National Institute of Biomedical Imaging and Bioengineering (NIBIB), Bethesda, MD; the University of Iowa, Iowa City, IA; and National Institute of Science and Technology (NIST), Gaithersburg, MD.

49. Develop tools to make LASIK and other ophthalmic surgeries safer and more effective

Challenge: Although objective measurements have demonstrated the more than 95% success rate of LASIK surgery, FDA has received some 140 letters of complaint from patients about post-LASIK symptoms, which have affected their quality of life. Complaints range from dry eye—the most common—to vision difficulties while driving at night.

Project: Develop a new tool (e.g., a quality of life survey) that can be used to help assess quality of life consistently and increase safety and effectiveness by improving patient selection to improve LASIK laser evaluation and other ophthalmic interventions.

Since the mid-1990s, LASIK surgery has been performed on some 7.6 million people in the United States. About 700,000 LASIK procedures are performed in the U.S. annually—including on 112,500 military personnel. Although an FDA panel reports a 95.4% satisfaction rate among people who have undergone the procedure, the Agency has received some 140 letters of complaint from patients about post-LASIK symptoms that have affected their quality of life (QOL). [26] FDA conducted a postmarket assessment of LASIK in 2006. It determined that QOL issues have not been evaluated consistently during premarket studies of LASIK lasers, and that few reports exist of well-designed post-LASIK QOL studies. FDA is collaborating with leading ocular experts on this three-year project to develop a plan for a QOL post-LASIK study. (FDA's Office of Women's Health has provided funding for the pilot study). The Agency is also creating a computer-based QOL survey to make available to the public a health-related QOL survey. The survey will be a compilation of previously validated questionnaires never before available in electronic format. It will allow QOL outcomes to be part of the pre- and postmarket evaluation of LASIK lasers, as well as possibly other ophthalmic products. FDA anticipates the QOL survey will enable better selection of patients to decrease the number of people with poor QOL outcomes after LASIK and other ophthalmic surgeries. The project's ultimate goal is to tackle the postmarket issue

[26] http://brighamandwomens.staywellsolutionsonline.com/RelatedItems/6,614914

and gain broad acceptance of the QOL survey. The hope is that the survey can be incorporated into standards and clinical trial design for premarket and postmarket device evaluation and be used by ophthalmic caregivers for managing their patients. A proposed computer-based QOL survey and protocol have been drafted and are nearly finalized. Study results and application to regulatory activities are expected in January 2011.

Project Collaborators: FDA; National Eye Institute, NIH, Bethesda, MD; American Society of Cataract and Refractive Surgeons (ASCRS), Fairfax, VA; American Academy of Ophthalmology (AAO), San Francisco, CA.

Center for Veterinary Medicine

The Center for Veterinary Medicine (CVM) took the lead on four projects receiving CPI funding during 2008.

50. Ensure the quality of the nation's food supply

Challenge: In 2007, the leading cause of bacterial food-borne infections were *Salmonella enterica* serotypes, and salmonella contamination continues to cause concern, most recently affecting some foods containing peanuts.

Project: Develop a test that can detect and characterize the salmonella serotypes involved in human and animal infections.

Knowledge of how *Salmonella* disseminates through the food chain is critical to understanding how food animals and food-processing procedures contribute to food contamination and human infection. FDA's Center for Veterinary Medicine (CVM) and Center for Food Safety and Nutrition (CFSAN) are working to design and use a cutting-edge, high-density microarray test that can detect and characterize 38 different *Salmonella* genomes that have been implicated in human and animal infections. The project goals are to identify new biomarkers, virulence factors, and antimicrobial resistance determinants that can be used to increase the timeliness and specificity of public-health monitoring of FDA-regulated food and animal feed products. To date, the microarrays have been designed and validated using a Salmonella reference collection, and the results presented at the Microbial Genomes Conference in September 2008. The project aims to publish related outcomes in a peer-reviewed journal and characterize more than 200 Salmonellae from the National Antimicrobial Resistance Monitoring System's (NARMS) retail meat collection during spring 2009.

Project Collaborators: FDA centers.

51. Encourage use of QbD in the manufacture of canine and human medicines

Challenge: To be safe, effective and cost efficient, pharmaceuticals must be manufactured with a consistent high quality and in large quantities. This is especially pertinent for drugs that are formulated as complex delivery systems. When questions about the safety of a therapy arise postmarket, the cause is often traced back to manufacturing problems.

Project: Facilitate the implementation of modern manufacturing approaches into the pharmaceutical manufacturing industry.

As medicine moves into the 21st century, product quality by design (QbD) is becoming increasingly critical to ensuring the safety, efficacy and cost containment of the rapidly evolving therapeutic landscape. FDA's CVM and CDER are working to create a roadmap for implementing QbD and other modern quality systems to better control product quality and consistency in the manufacture of medicines. The ultimate goal is to understand key variables when producing medicines used to treat canines and humans. Research currently under way is helping us understand the variables associated with raw materials or manufacturing processes through monitoring and controlling these variables online during manufacturing. This information can be used to establish product specifications that must be met by all product batches prior to release for marketing. The project objectives will be achieved by manufacturing several formulations of carefully selected drugs, using differing manufacturing process and sources of raw materials, and by generating information on physical and chemical characteristics of these products. Using an online monitoring system allows us to control the quality from upstream during the manufacturing. The final step will be to compare these performance data to the plasma drug concentrations resulting from the administration of these different formulations to dogs and people. The resulting in vitro and in vivo datasets will subsequently be evaluated by comparing the resulting mathematical description of the relationship between in vivo and in vitro product performance (in vitro-in vivo correlation (IVIVC)) in canine versus human subjects.

Project Collaborators: FDA; University of Maryland, College Park, MD.

52. Facilitate use of peptides in treating infections

Challenge: Antimicrobial peptides show promise as therapeutic agents, but to evaluate their safety and efficacy, FDA must understand their properties, function, and efficacy.

Project: Characterize and analyze bronchial antimicrobial peptides with the goal of identifying and studying antimicrobial peptides that aid in the defense against bacterial pneumonia in cattle.

Antimicrobial peptides are part of the in-born immune response and are found among all classes of life. These peptides are potent antibiotics that offer great potential as new therapeutic agents. For example, peptides have been shown to kill many types of micro-organisms, even some that are resistant to conventional antibiotics, and they contribute to defense against infection at many sites in the body. Unlike most conventional antibiotics, antimicrobial peptides may also be able to enhance immunity. Humans and cattle share several peptide classes that may be important in combating infections. These compounds are being developed for therapeutic uses in people and animals. It is essential that FDA understand the properties, function, and efficacy of these peptides. To support this goal, CVM and CFSAN are working together to characterize and analyze bronchial antimicrobial peptides using an animal pneumonia model. Research goals include identifying and studying several antimicrobial peptides that aid in defending against bacterial pneumonia in cattle. As of October 2008, at least three peptides have been identified that are known to have bacteria-killing functions. Several other peptides of interest have also been found, and their functions are being confirmed. Testing began in late 2008 on the purified peptides for their ability to kill several disease-causing bacterial strains in a laboratory setting. The project will then communicate the results to the FDA laboratory as well as review scientists and stakeholders through presentations at conferences and peer-reviewed publications.

Project Collaborators: FDA centers.

53. Improve FDA's ability to assess safety and efficacy of veterinary drugs

Challenge: FDA must rely on very limited datasets for establishing product safety and effectiveness of veterinary medicines due to economic imperatives associated with developing veterinary drugs.

Project: FDA is working to define alternative test methods to improve population predictions derived from clinical safety and effectiveness data.

The economic limitations associated with developing veterinary drugs mean that FDA must rely on very limited datasets for establishing product safety and effectiveness. To strengthen its evaluation efforts, FDA's CVM and CDRH have launched a project to develop an alternative test method to improve the drug development process for clinical safety and effectiveness studies. The project is studying the pharmacogenomics (the study of how an individual's genetic inheritance affects the body's response to drugs) of the multi-drug

resistant MDR-1 protein. This protein transports a wide variety of drugs, including heart worm medications, chemotherapeutic drugs, opiates, and steroids, in and out of various cells in the body, including the brain. Herding dogs, including some collies, are known to have a mutated form of the MDR-1 that results in a non-functioning transport protein. This defect results in toxicity to drugs that are normally safe for dogs. Heartworm drugs such as ivermectin are especially toxic to dogs that have a mutated MDR1 protein. This is why the current drug approval process for new heartworm medications requires companies to demonstrate the safety of these new drugs in ivermectin-sensitive collies. However, because of the scarcity of ivermectin-sensitive collies, the safety of other new veterinary drugs that might be transported by MDR-1 are not being evaluated and their potential toxicity is unknown.

Part 1 of this three-year study is evaluating the genotypic and phenotypic effects of different p-glycoprotein substrates given to normal and ivermectin-sensitive collies. (Genotype refers to an organism's fundamental constitution in terms of its hereditary factors and phenotype refers to what an organism looks like as a consequence of the interaction of its genotype and the environment). Part 2 of the study will develop a genetically modified mouse model that has this particular mutated dog gene. The goal is to replace the ivermectin-sensitive collies with the genetically modified mouse model when drugs transported by MDR-1 are being evaluated. Development of the mouse model will replace the use of ivermectin-sensitive collies with a less expensive animal model, which will also provide useful information faster than the current paradigm. This study will expand the inferential value of data included in new animal drug applications by testing the impact of the MDR-1 gene mutation on drug safety issues early in the drug discovery process in a more economic and safer manner. Understanding the pharmacogenomics of a new drug and the potential for toxicity in animal subpopulations will improve the Agency's ability to predict a new drug's safety and effectiveness.

Project Collaborators: FDA centers; Precision Biomarker Resources, Inc., Evanston, Il; IO Informatics, Inc., Berkeley, CA; genOway, Lyon, France.

Center for Food Safety and Nutrition

The Center for Food Safety and Nutrition (CFSAN) took the lead on two projects receiving CPI funding during 2008.

54. Improve FDA's ability to use existing information to streamline safety evaluation and respond to emergency contaminations

Challenge: It is critical that FDA be able to respond rapidly and thoroughly to product contamination emergencies while meeting aggressive statutory timelines for food additive reviews.

Project: Develop tools for rapid risk analysis of potential food and drug contaminations.

Alarm over melamine-contaminated food ingredients and other food and drug safety scares have underscored the public health need for a robust emergency response to product contamination. Such an effort requires the ready availability of safety-relevant data and software tools for analyzing that data.

Likewise, aggressive statutory timelines for the premarket review of food ingredients have created a need to provide computational toxicology support for more timely and systematic safety decisions. Additionally, the need for risk analysis in short time frames to support emergency response to food, food ingredient, and drug contamination requires that preclinical and clinical data relevant to safety as well as tools for analyzing that data be immediately available at the FDA reviewer's desktop.

The boom in the design and use of predictive toxicology software to develop and evaluate drugs, industrial chemicals, and food additives during the past decade has given FDA the ability to harness a new level of decision support and improve its efforts to ensure the safety of food ingredients. FDA's CFSAN and CDER are working to accelerate and expand their work to harvest FDA's vast trove of toxicity information and convert it into toxicity databases. The goal is to capture electronically most of the data submitted to the Agency on foods and drugs. Compilation of these data should pave the way for development of a suite of computational analytical toxicology software that could be used to provide additional decision support beyond the safety data submitted to CFSAN.

Project Collaborators: FDA; Leadscope, Inc., Columbus, OH.

55. Reduce chronic disease by identifying more predictors of disease risk

Challenge: We have identified a limited number of predictors of disease risk, called *modifiable risk biomarkers* or *surrogate endpoints*, that can be modified by factors like diet, lifestyle, and drugs. But most modifiable risk biomarkers for chronic disease risk have not been qualified for use as health claims by FDA in a drug marketing application. More of these biomarkers are needed for chronic diseases like cancer, heart disease, and diabetes.

Project: Develop a framework for validating modifiable risk factors or biomarkers for more chronic diseases. Identify and qualify new modifiable biomarkers that can be the subject of a health claim or qualified health claim.

FDA and the National Institutes of Health (NIH) have identified certain predictors of disease risk, called *modifiable risk biomarkers*, for a limited number of chronic diseases:

- Total and low-density lipoprotein cholesterol and blood pressure for coronary heart disease
- Elevated blood glucose and insulin resistance for diabetes
- Mild cognitive impairment for dementia
- Bone mineral density or bone mineral content for osteoporosis
- Adenomatous colon polyps for colon/rectal cancer

But there are many other diseases for which we have no validated modifiable risk biomarkers. Expanding the knowledge base of predictors of disease risk would enable us to prevent or mitigate more chronic diseases through modification of diet and lifestyle or the use of medicines. Early detection of chronic disease risk also results in major cost savings since interventions like change of diet and lifestyle or drug therapy are far cheaper than treating a chronic illness like coronary heart disease. Thus, the goal of this research, initiated in September 2008 through a contract with the Institute of Medicine (IOM), is to develop a framework for validating modifiable biomarkers for chronic diseases that can serve as a health claim. The IOM is convening an expert panel to review scientific data and findings related to biomarker qualification standards to determine potential surrogate endpoints. The contract's outcome will be a final report, submitted to FDA by May 2010, which will include the findings and recommendations resulting from the panel's assessment. FDA will use this information both to create a process for qualifying biomarkers as potential surrogate endpoints of chronic disease risk and in reviewing health claims and drug approvals.

Project Collaborators: FDA, Institute of Medicine (IOM), Washington D.C.

National Center for Toxicological Research

The National Center for Toxicological Research (NCTR) took the lead on 5 projects receiving CPI funding during 2008.

56. Expand FDA's ability to receive and analyze –omics data

Challenge: Substantial amounts of complex pharmacogenomic data are being submitted to FDA as part of the application review process. But the Agency lacks the necessary integrated bioinformatics infrastructure to evaluate these data efficiently.

Project: Develop an integrated informatics infrastructure at the Agency that will enable FDA reviewers to effectively and efficiently evaluate these data.

Increasingly, sponsors are submitting pharmacogenomics and other types of –omics data (e.g., proteomics and metabolomics data and data from genome-wide association studies) to FDA as part of their applications for drug approval. These types of data will help to individualize treatments, making them safer and more effective. However, *pharmacogenomics* uses technologies that generate a tremendous amount of complex data, constituting a formidable challenge for regulatory review. In addition, since receiving the first voluntary genomics data submission, FDA has seen a shift in technologies, from the use of largely DNA microarray data to the use of non-microarray pharmacogenomic data. FDA needs an efficient and integrated informatics technology infrastructure to:

- Review and understand how sponsors reach their biological conclusions
- Enable effective interactions with sponsors
- Ensure that pharmacogenomic data are incorporated into regulatory processes so as to achieve the public health benefits

ArrayTrack, a key bioinformatics tool used in FDA's pharmacogenomics program can evaluate only DNA microarray data. FDA is working to expand this tool to enable the evaluation of non-microarray pharmacogenomic data. The project will create new modules in ArrayTrack to make evaluation of all such data possible. The study will also create modules to make it easier to submit both animal study data and –omics data to FDA electronically.

Project Collaborators: FDA; Ingenuity, Redwood City, CA; GeneGo, St. Joseph, MI; SAS Institute, Cary, NC; Rosetta Biosoftware, Seattle, WA.

57. Build FDA's infrastructure to electronically receive, manage, analyze, and communicate information on FDA-regulated products

Challenge: The concept of creating a wholly electronic infrastructure to manage information submitted to FDA has never been formally analyzed, nor have existing electronic components been assessed for functionality.

Project: Run a pilot that studies the potential for electronic data submissions to improve Agency efficiencies.

FDA and sponsors have recognized that developing an electronics data submission (e-submission) environment is a vital step in the Agency's future regulatory data submission process. Although several collaborative efforts are under way between industry and FDA to facilitate this process, the concept itself has yet to be tested. FDA's NCTR and CDER in collaboration with the Agency's Office of Critical Path Programs, participating companies and platform providers have launched a pilot project to conduct an electronic data submission study for improving the efficiency of FDA's review process. The study is using clinical and preclinical data submissions to determine the effectiveness and utility of existing e-submission concepts, identify key bottlenecks and limitations of e-submission strategies, and specify improvements and best practices to provide an effective e-submission process at each stage of the submission pipeline. Lessons learned from the study will enable process deficiencies to be detected and rectified, thus laying the groundwork for rolling out the e-submission environment in the Agency. The pilot project has two parts: a non-clinical regulatory e-submission study, using the existing e-submission platform ToxVision, and an investigation of the validity of the existing e-submission proposals for both clinical and nonclinical data as well as pharmacogenomics data through the FDA Voluntary Genomics Data Submission project.

Project Collaborators: FDA; Clinical Data Interchange Standard Consortium (CDISC), Austin, TX; and the National Cancer Institute (NCI), Bethesda, MD.

58. Develop biomarkers to assess the potential of drug-induced genetic damage during clinical trials

Challenge: Biomarkers that could be directly measured in humans could improve our ability to evaluate the safety of candidate therapies based on clinical trial results.

Project: Develop a pig-A gene mutation assay for use in pharmaceutical safety testing during clinical trials, the results of which will lead to a model that can be used in humans to determine if the candidate drug being tested could cause genetic damage.

The safety evaluation of drugs intended to treat humans relies on a battery of in vitro and rodent-screening tests to determine potential genetic damage before candidate drugs are administered to humans (preclinical testing). Test results are then used to determine whether a candidate drug is safe for phase 1 clinical trials in healthy people. But new, more sensitive approaches are needed to provide a more accurate determination of possible human risk. Biological indicators—or biomarkers—that could be directly measured in humans could improve our ability to evaluate the safety of candidate therapies before using them in humans. FDA is working to develop a pig-A gene mutation assay for use in pharmaceutical safety testing during clinical trials. This effort will lead to a model that can be used in humans, similar to FDA's recently developed rodent model, in which a mutation can be rapidly detected using a small sample of blood. Such a mutation biomarker can then be validated and used in humans during clinical trials to determine if the candidate drug being tested could cause genetic damage. The project is set to be completed within its two-year timeframe.

Project Collaborators: FDA; Teijin Pharma, Tokyo, Japan; University of Vermont, Burlington, VT; BioMosaics, Burlington, VT; and Litron Laboratories, Rochester, NY.

59. Expand our understanding of drug-related liver damage

Challenge: Many of the drugs on the market that ultimately fail and many of the drugs that fail during clinical trials do so as a result of liver toxicity.

Project: Create a repository of known information on liver toxicity to support research on the subject early in clinical trials.

More than 25% of drugs on the market that ultimately fail and 40% of drugs that fail during clinical trials do so because of liver toxicity. Although enormous efforts are under way to explore genomic methodologies and other biomarker identification technologies to detect drug-induced liver toxicity, research in this field is hindered because no comprehensive hepatotoxicity-centered knowledge base exists that aggregates known information. Such a content-rich resource needs to be developed both for research and regulation. FDA is working to develop a liver toxicity knowledge base (LTKB) that can support research to uncover relationships among diseases, pathways, genes/proteins, and drugs, using data from biomedical literature and other public resources. The LTKB will help fill a major gap in research and regulation related to hepatotoxicity. The project will:

- Identify liver toxicity-related genes/proteins, pathways, chemicals, and diseases by mining more than 18 million abstracts in *PubMed* and other public resources
- Annotate the genes/proteins, using in-house ArrayTrack, the Cancer Genome Anatomy Project (cGAP), and other public resources to create a database
- Annotate the knowledge accumulated to develop a set of training rules
- Establish a knowledge base to develop liver toxicity-related regulatory networks and association of genes/proteins-pathways-chemicals-diseases

The LTKB will be augmented with public -omics data, such as gene expression profiles and data from collaborators.

Project Collaborators: FDA; The Environmental Bioinformatics Institute, University of Medicine and Dentistry, Newark, NJ; and Fraunhofer Institute of Toxicology and Experimental Medicine, Hannover, Germany.

60. Develop consensus on standards for using microarray data in personalized medicine and in the discovery, development, and review of FDA-regulated products

Challenge: A microarray is an important method for profiling gene and protein expression in cells and tissues. However, the scientific community has expressed concerns about the reliability of predictive models developed from microarray data.

Project: Coordinate a consortium to address the technical and data analysis challenges involved in the appropriate use of microarray data.

The MAQC Phase II project aims to reach consensus among more than 300 scientists from more than 150 organizations worldwide—including FDA, the Environmental Protection Agency, NIH, NIST, academic laboratories, and industrial partners—on the best practices for developing and validating predictive models for clinical (diagnosis, prognosis, and treatment outcome) and preclinical (toxicogenomics) applications. FDA has identified DNA microarrays as a key tool for advancing medical product development and personalized medicine through identifying and qualifying biomarkers of efficacy and safety. However, concerns have been raised in publications[27] about the reliability of microarrays. This project will:

- Assess the reliability of microarray-based predictive models for clinical and preclinical applications
- Submit consensus recommendations to the microarray community on the critical component of personalized medicine
- Pave the way for microarray data to be applied appropriately in the discovery, development, and review of FDA-regulated products

Project Collaborators: FDA; EPA, Washington, D.C; National Institute of Environmental health Sciences (NIEHS), Research Triangle, NC; NCI; NIST, Bethesda, MD; University of Arkansas for Medical Sciences, Little Rock, AR; Anderson Cancer Center, Houston, TX; University of Cologne, Cologne, Germany; Millennium Pharmaceuticals, Cambridge, MA; SAS Institute, Cary, NC; Systems Analytics, Waltham, MA; Affymetrix, Santa Clara, CA; Illumina, San Diego, CA; Agilent, Santa, Clara, CA.

[27] e.g., Marshall E, *Science* 306, 630 (2004).

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