Critical Path Initiative
Food & Drug Administration

The critical path initiative

Report on Key Achievements in 2009

Transforming the way FDA-regulated products are developed, evaluated, and manufactured

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Introduction

The Critical Path Initiative is FDA's strategy for driving innovation in the way its regulated products are developed, evaluated, and manufactured. Launched in March 2004 to tackle the *pipeline problem*, the Initiative (CPI) strives to narrow the gap between the number of discoveries occurring in biomedical science and technology and the declining number of new medical treatments submitted for FDA approval.

Cutting-edge advances in medical science demand 21st century tools and processes for translating discoveries into new and better therapies. This means modernizing the nation's outdated clinical models, scientific methodologies, manufacturing practices, and paper-based infrastructure — making the pathway from medical discovery to treatment more efficient and cost effective.

But creating this new paradigm cannot be done by any one entity. It requires all stakeholders — government, industry, academia, and consumers — to collaborate in delivering on the promises of scientific research and technology.

As a neutral, noncompetitive organization, FDA is uniquely positioned to serve as a catalyst in driving collaboration and innovation. We do this by building partnerships and creating new opportunities for industry and other stakeholders to share expertise and data about more effective and safer ways to develop medical products.

Today, CPI is supporting research projects across the Agency, largely through partnerships that include other Federal agencies, academia, industry, and other public health-related organizations. CPI applies collaboration, information management, science, and standards development, among other tools, all along the critical path of medical product development, evaluation, manufacture, and use to:

- Identify and qualify biomarkers that can personalize therapy and make clinical trials more efficient and safer
- Help develop new diagnostics and treatments
- Apply cutting-edge quality-by-design methods in pharmaceutical manufacturing
- Introduce information technologies into medical product development and postmarket surveillance

CPI's goal is more efficient medical product development and evaluation as well as improved quality, safety, and effectiveness of the products FDA regulates.

Recent Successes

FDA is often asked to describe Critical Path Initiative successes and their significant public health outcomes. The following section provides a brief snapshot of Critical Path achievements in three areas: biomarker development and qualification (and personalized treatment), modernizing clinical trials, and improving product safety.

Developing Biomarkers and Other Scientific Tools

- Collaborative research into the genetics of people using ***warfarin*** (Coumadin) led to the 2007 addition of supplementary dosing information to warfarin labels.
- The discovery of genetic markers in people using ***clopidrogrel*** (Plavix) resulted in the 2009 addition of dosing information to labels. (After more research into the data, in early 2010, FDA highlighted this information in a boxed warning).
- In early 2010, the ***International Serious Adverse Events Consortium***, a nonprofit partnership of 10 international pharmaceutical companies and academic institutions, announced the release to the public of data on the genetics associated with adverse events (negative side effects), specifically, drug-induced liver injury and drug-related serious skin reactions, such as Stevens-Johnson syndrome. Drug-induced liver injury occurs in a small subset of patients and is usually associated with a drug that is an unpredictable liver toxin. Serious skin reactions like Stevens-Johnson present as allergic skin reactions and can be fatal if the signs and symptoms are not quickly recognized. These data will help researchers better predict an individual's risk of developing these serious complications.
- ***The Predictive Safety Testing Consortium***, a public–private partnership led by the non-profit organization the Critical Path Institute (C-Path), supports the sharing of data by industry to receive, review, and approve new tools as *qualified* for use in drug development. This effort is taking place under the advisement of FDA and the European Medicines Evaluation Agency. In May 2008, FDA and EMEA confirmed their joint review and acceptance of seven new biomarkers (i.e., laboratory tests on urine that signal kidney injury). These new tests can now be used in laboratory research to predict the safety of experimental drugs.
- In a collaboration among private- and academic-sector partners and FDA, a repository of digital ECGs (electrocardiograms), ***the ECG Warehouse***, has been created that is being used to study the cardiac toxicity of drugs.

Streamlining Clinical Trials

- FDA launched a broad-based collaboration (the Clinical Trials Transformation Initiative, CTTI) with Duke University to "modernize the U.S. clinical trials enterprise." At last count, 48 representatives from academia, professional societies, patient and consumer groups, and industry, among other Federal agencies are seeking new methods and tools to make the current system more efficient.
- In November 2009, CTTI and FDA sponsored the first of CPI's annual three-day training course for clinical trial investigators, drawing 125 participants from around the world.
- In February 2010 FDA issued two draft guidances making recommendations on innovative trial designs (adaptive and non-inferiority designs).

Ensuring Product Safety

- Prescription drug labels are being made available electronically on the Internet free of charge (DailyMed, ***more than 8,500 prescription drug labels are now accessible***); ultimately labels for all products will be available.
- In late fiscal year 2009, FDA competed and awarded a contract to Harvard Pilgrim Health to pilot a miniature Sentinel System (*Mini-Sentinel*), with a coordinating center, to test the scientific operations and develop methods needed for the ultimate Sentinel System.
- Ongoing cooperative efforts with CMS and ASPE have been expanded to include other Federal partners (VA, DoD) (***Federal Partners pilot***) to develop active surveillance methodologies and conduct "medical product-adverse outcome" queries.
- ***SafeRx***, a collaboration among CMS, FDA, and ASPE is up and running, enhancing FDA's existing safety surveillance capacity and providing close to real-time vaccine safety monitoring of seasonal and H1N1 influenza vaccines.
- In 2009, FDA was pivotal in establishing the DAPT Collaboration to design and conduct a postmarket study of drug-eluting stents. Launched in September 2009, under the management of Harvard Clinical Research Institute, this industry study is comparing two different durations of treatment after placement of a coronary stent; 12 months vs. 30 months on the antiplatelet medication while continuing on aspirin. By leveraging the shared resources of all participants (including four drug and four device firms), this study will give the global medical community the information it needs to devise appropriate treatment recommendations for the duration of antiplatelet therapy in patients implanted with drug-eluting stents, thus improving the safety of patients who receive these implants. This multicenter trial will enroll approximately 20,000 patients at 220 centers in North America and Europe.

Progress in Specific Project Areas

In contrast to CPI's previous reports, which listed and briefly described CPI-identified projects, the 2009 report features a more detailed look at some of the most exciting CPI projects underway. The report illustrates the diversity and complexity of Critical Path work and emphasizes its related public health outcomes.

This 2009 report demonstrates how new, scientific tools and processes can lead to direct public health outcomes while fostering future discoveries.

Modernizing the Clinical Trial Enterprise — Clinical Trials Transformation Initiative — *The success of the U.S. clinical trial system hinges on the public's confidence in its safety, integrity, and transparency. Streamlining U.S. clinical research practices — while bolstering patient safety — is essential for making new, safer, and more effective medical products available to the nation*

Background—The Outdated Clinical Trial Model

Patients and their caregivers need access to new medical products as quickly as possible, with the assurance that the benefits of their use outweigh the risks. But our current clinical trial system employs many of the processes of the last century—often paper-based, slow, and costly.

As evolving technologies and new areas of science fuel an increase in the number and complexity of trials, it is vital that clinical research keep up with these developments. Poor quality and inefficiency in clinical research can seriously limit the questions we can answer about the uses of marketed medical products and significantly delay access to innovative therapies.

Of mounting concern as well is the fact that clinical trials are increasingly moving outside of the United States. The reasons behind this shift need to be understood and addressed so that U.S. patients can continue to be represented in international clinical trials, since their participation is critical to address the appropriate use of products by Americans.

CTTI Formation and Achievements

In 2007, these concerns led FDA and Duke University to launch the Clinical Trials Transformation Initiative (CTTI) — a unique public–private partnership that brings together diverse stakeholders[1] in the clinical trial industry with a

[1] CTTI comprises some 50 organizations, including government agencies (FDA, Centers for Medicare & Medicaid Services, Office of Human Research Protections, National Institutes of

mission to identify practices, which, through broad adoption, will transform the quality and efficiency of clinical trials.

To achieve this goal, CTTI conducts projects to generate empirical information about how clinical research is currently conducted and to identify and test ways to improve quality and efficiency. An overview of current CTTI projects follows.

Effective and Efficient Monitoring

The project goal is to identify best practices and develop sensible criteria to help sponsors choose the most appropriate monitoring methods for a trial, thereby improving quality while optimizing the deployment of resources. The project team has explored a range of monitoring practices in use and the factors driving their adoption. Various stakeholders met in autumn 2009 to reach consensus about key quality objectives for monitoring. An evaluation of the practice strengths and weaknesses in meeting quality objectives over a range of clinical trial settings is underway.

Improving SAE Reporting to IND Investigators

This project is generating empirical evidence about the current U.S. system for reporting serious adverse events (SAEs) to investigators under an investigational new drug application. The goal is to consider potential system modifications that more efficiently and effectively inform investigators of such events. The project includes five subprojects:

- Document the range of sponsor practices for reporting unexpected SAEs to investigators and for oversight of product safety (e.g., safety committees)
- Quantify investigator time spent receiving, interpreting, and communicating individual expedited reports and assessing perceived value to investigators of individual expedited reports in updating a product's risk profile
- Compare the current practice of submitting individual SAEs to an alternative approach based on a European Commission's guidance
- Study patient expectations about monitoring and communicating product safety during the conduct of a clinical trial
- Convene expert group to integrate results and recommend ways to optimize SAE reporting to investigators and ensure subject protection

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Health, and other national and international government bodies), industry representatives (pharmaceutical, biotech, device, and clinical research organizations), patient and consumer representatives, professional societies, investigator groups, academic institutions, and other interested parties.

New Projects

The CTTI Steering Committee (including one representative from every member organization) is developing several project ideas into project plans for consideration as new CTTI undertakings.

Collaborations

CTTI collaborates with other organizations in educational and research initiatives to improve clinical trials.

- **Use of Clinical Trials in Evaluation of Comparative Effectiveness**

In May 2009, CTTI convened an expert meeting in collaboration with the Pragmatic Approaches to Comparative Effectiveness (PACE) Initiative and the Center for Medical Technology Policy (CMTP) to discuss with policy-makers the premise that randomized controlled trials would be more commonly used for comparing the effectiveness of medical products and procedures if (1) operational efficiency was improved, (2) Bayesian adaptive principles were applied to trial design, and (3) the needs of decision-makers were addressed by more pragmatic trial designs that increased the ability to generalize results. Representatives from CTTI, CMTP, and PACE were charged with developing an article for the *Annals of Internal Medicine* on the need for transformational changes in clinical trials to meet the requirements of comparative effectiveness research.[2]

- **Standards for Collecting Data on Cardiovascular Events**

CTTI is participating in a collaborative pilot project with FDA and other organizations to develop standard definitions and data collection methods for cardiovascular events in clinical trials. (This effort has relevance for other therapeutic areas because, increasingly, cardiovascular outcomes are being evaluated during the development of a variety of new biologics, devices, and drugs). The project goal is to provide uniformity for endpoint reporting, adjudication, and data collection so that results from clinical trials can be analyzed more easily and trends and other safety signals identified.

- **FDA Clinical Investigator Training Course**

FDA and CTTI launched the first, annual, three-day training course for clinical investigators on scientific, ethical, and regulatory aspects of clinical trials. The inaugural course was held November 16–18, 2009, in Silver Spring, Maryland, attracting participants from around the world. The next course is planned for November 2010.[3]

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[2] Luce BR, Kramer JM, Goodman SN, Connor JT, Tunis S, Whicher D, Schwartz JS. Rethinking randomized clinical trials for comparative effectiveness research: the need for transformational change. Ann Intern Med. 2009;151:206–9.

[3] Course details and registration information can be found on the event Web page at: https://www.trialstransformation.org/fda-clinical-investigator-training-course/). For more information about these projects and collaborations, please visit the CTTI Website (www.trialstransformation.org).

Leaving the Paper-Based World Behind — *Creating an all-electronic environment for managing data on FDA-regulated products*

FDA is harnessing information technologies (IT) to move from a paper-based environment to a fully automated organizational model, empowering the Agency to manage the huge amounts of data it receives on regulated products more efficiently and effectively. The paper-based infrastructure on which FDA has depended for nearly a century cannot support the demands of a globalized economy and the sophisticated analysis required for innovative therapies. FDA relies increasingly on the electronic submission and evaluation of this data. For example, the Agency depends on IT systems to assess medical product safety and effectiveness during the review of marketing applications; to receive reports of adverse events for products on the market; and to communicate vital safety information to the public.

Systems modernization requires overhaul in three major information management domains: **access**, **standards**, and **interface**. Greater access to information, more standardized formats, and better interface with data are the key tools of empowerment that the Agency requires to convert into knowledge the ever-escalating volume of information it receives.

FDA's Agency-wide informatics team has been working with stakeholders for more than a decade to devise and implement standards and systems that will enable the electronic receipt, management, and storage of FDA-regulated product information. In fact, marketing applications, drug labels, and adverse event reports are now being submitted electronically.

A colossal effort such as this requires enormous time and resources. The recent move toward a universal electronic health record makes it all the more imperative that FDA be able to leverage IT to execute its mission.

2009 Achievements

Some of the many project accomplishments of 2009 are highlighted here.

- **Janus** is a major pilot repository to manage and store study data[4]

FDA and the National Cancer Institute (NCI) are building the Janus study data repository through the Interagency Oncology Task Force (IOTF). This partnership is enabling the two organizations to share knowledge and resources. FDA has been able to build tools and an environment that streamlines electronic interaction and collaboration among FDA and its stakeholders in the regulatory review process. The Janus data repository is part of a larger effort to implement a common, standards-based electronic

[4] This project was approved by FDA's Bioinformatics Board. Representatives from all Agency centers and numerous offices are closely involved.

infrastructure that underpins the submission, validation, data warehousing, access, and analysis of study data.

In 2009, FDA contributed to Phase 2 of the Janus operational pilot project, collaborating with NCI on developing a data validation and import facility, loading validated standardized clinical datasets into the Janus repository, and creating analytical views that could be accessed with reviewer tools.

Also during this period, the Office of Critical Path Programs (OCPP) and the Agency's National Center for Toxicology Research (NCTR) worked on creating and testing the Janus 2.0 data model. The model is the blueprint for the Janus repository, where FDA plans to store and manage study data about the products it regulates.

This enhanced Janus repository will not only support clinical (human) study data (as in the Janus prototype currently at NCI) but also accommodate nonclinical study data (e.g., animal toxicology data, product and device data), thereby enabling more effective and efficient reviews.

- **Drug establishment registration and drug listing**

This electronic system became fully operational in the summer of 2009. It receives and manages key data on pharmaceutical manufacturing facilities and the medicines they produce.[5]

- **Multiple standards development activities**

OCPP continues to lead the development and testing of exchange standards that are fundamental to the future of information technologies. Exchange standards provide a consistent way to pass information between computer systems in various organizations, ensuring that the sending and receiving systems both understand unambiguously what information is being exchanged (this is known as semantic interoperability).

OCPP is also developing and maintaining terminology standards that provide a consistent way to describe concepts. For example, FDA is creating and maintaining the Unique Ingredient Identifiers (UNII), which provide a consistent means of describing substances in foods and drugs.

- **ToxVision** and **PGx pilots** to encourage electronic submission of nonclinical toxicology and pharmacogenomics data

These pilots involve the electronic submission of nonclinical toxicology data based on the SEND standard (Standard for the Exchange of Nonclinical Data) and voluntary submission of pharmacogenomics data.

[5] This project was approved by FDA's Bioinformatics Board.

Toxicology data are received from sponsors via the FDA electronic gateway. Received data are validated and loaded into a database at FDA's National Center for Toxicological Research. Reviewers in the Center for Drug Evaluation and Research are able to log into a Web-based program (ToxVision) to view and analyze the data. Pharmacogenomics (PGx) data are submitted voluntarily to FDA and stored and analyzed via ArrayTrack. This pilot combines the genomics data with its corresponding (both clinical and nonclinical) study data for analysis beyond what is available when the data types are examined independently. The pilots are expected to be complete in summer 2010. Findings will be shared with the public.

2010 - 2013 Goals:

Outlined below are just some of FDA informatics goals for the next three years:

- Enhance the Structured Product Labeling (SPL) standard, which gives public access to the latest product labeling information (e.g., through pictures that aid in identifying a drug in cases of accidental overdose, counterfeiting investigations, and patient and physician education)
- Develop Phase 3 of Janus, an operational environment for validating, loading, storing, extraction, and access to analytical tools to support review of products under FDA purview
- Provide leadership and resources to FDA's participation in Comparative Effectiveness Research (CER) as part of the American Recovery and Reinvestment Act (ARRA) funding. (The Department of Health and Human Service's goal for this program is to promote high-quality care through broad availability of information that helps clinicians and patients match the best science to individual needs and preferences.) This funding makes possible the development of an infrastructure that will enable FDA to harness the capacity of the Janus repositories to conduct more robust analyses for detecting clinical trends. Such enhanced capabilities will enable us to determine which interventions are most effective for which patients under specific circumstances.
- FDA will receive nonclinical review data from sponsors in electronic form, based on the latest SEND version.
- CDER pharmacology toxicology reviewers will conduct reviews electronically using the ToxVision software.

Modernizing Pharmaceutical Manufacturing — *to ensure the quality of medicinal products in a globalized economy. Developing 21st-century tools will enable the performance of automated sampling and analysis of biotechnology products*

FDA encourages the use of tools, such as process analytic technology (PAT), during the manufacturing of medicines as an efficient way to ensure their quality. PAT involves designing, analyzing, and controlling pharmaceutical manufacturing processes in real-time (i.e., at-line, in-line, or on-line). This approach to manufacturing has reduced over-processing and enhanced manufacturing consistency. It minimizes rejects in traditional pharmaceutical manufacturing. In 2008, FDA began exploring the development of PAT tools that can be used during the manufacture of biopharmaceutical products (e.g., monoclonal antibodies and recombinant proteins) to help ensure quality. The project builds on existing work in the cell culture bioprocess area with the University of Maryland.

2009 Achievements

In 2009, achievements include:

- Publication of a comprehensive survey of industry practices on implementation of PAT in bioprocessing and biotechnology
- Collection of information from regulatory submissions into a database to help analyze current industry experience and practices on glycoforms in monoclonal antibodies and related products
- Commencement of analysis and optimization of antibody-producing cell lines
- Prototyping an integrated bioreactor system with automated sampling and product analysis using chromatography

Goals Planned for 2010

Additional projects are planned for 2010:

- Use the integrated bioreactor system to demonstrate at-line monitoring tools for monoclonal antibody quality attributes and product titer
- Analyze the regulatory submission database for glycosylation and functional information. Publish an overview of current industry practices to characterize glycoforms in monoclonal antibodies and related products. Characterize the influence of glycosylation on biological activity of these products
- Develop and demonstrate tools to directly analyze glycoform-related quality attributes in real time from bio-reactor samples

Liver Toxicity Knowledge Base (LTKB) *to empower the FDA review process*

Liver toxicity is the cause of some 40% of drug failures in clinical trials and 27% of market withdrawals. Huge efforts are under way — involving genomic methodologies — to explore techniques to identify biomarkers that could help in detecting drug-induced liver toxicity. However, research in this field has been hindered because a comprehensive hepatotoxicity-centered knowledge base is not available that can aggregate known information.

In 2008, FDA began building this knowledge base — the Liver Toxicity Knowledge Base (LTKB) — which can support research to reveal relationships among diseases, pathways, genes/proteins, and drugs, using data from biomedical literature and other public resources. In addition to being useful to FDA during the review of marketing applications, the LTKB will be an invaluable tool during research into the cause and prevention of drug-related liver toxicity.

2009 Achievements

A number of milestones were achieved in 2009:

- More than 18 million manuscript abstracts were downloaded for assessment of drug-induced liver injury.
- A text mining tool, called TexTrack, was created to extract specific information about liver injury from these abstracts.
- Standard data sets were developed that contain information on ~200 drugs for study of drug-induced liver injury.
- Cell-based toxicity assays (test systems) for the standard datasets have been conducted.
- Microarray assays for 60 drugs were completed.

2010-2011 Goals

- Continue the curation process for liver toxicity data from literature
- Conduct a meta-analysis on the genomics data collected from the literature
- Analyze the microarray data and other types of data generated from this project

New Toxicology Tools for Use in Clinical Trials — *develop a gene mutation assay to test for safety in humans during clinical trials, reducing the uncertainties of safety testing in lab animals*

Better assessment tools for identifying genotoxic hazards[6] associated with pharmaceuticals are needed to facilitate the development and approval of new treatments. Research into pharmaceuticals using surrogate test systems (i.e., in animals) indicates that an increase in gene mutation is associated with a risk of cancer. If we could safely measure gene mutation directly in humans, we could eliminate the uncertainties associated with preclinical drug safety assessments in laboratory animals in predicting safety in humans.

In mid 2008, FDA launched a collaborative research project with academia and industry to develop a model for detecting mutation in the endogenous phosphatidyl inositol glycan, class A, gene (*PIG-A*) and to study the possibility of using this tool in humans for measuring potential genotoxic hazards. A protocol and two test systems were developed for detecting *PIG-A* mutant red blood cells and assayed blood samples from normal healthy donors.

2009 Achievements

Achievements during 2009 include:

- Continued development and evaluation of FDA's red blood cells assays
- Using these optimized assays, established that most healthy humans have very low *PIG-A* RBC and granulocyte mutant frequencies and thus *PIG-A* mutation measurement may be a sensitive method for detecting exposure to potentially carcinogenic drugs
- Began the study's third phase, which involves evaluating the sensitivity of the mutation detection model by measuring *PIG-A* mutant frequencies in pre- and post-treatment samples from a series of six cancer chemotherapy patients
- Shared preliminary findings at relevant meetings

2010-2012 Goals

- Measurements will continue through 2010 on these patients and on four additional patients as stipulated in the project protocol.
- When completed, the results will be used to evaluate the assays' ability to measure the mutagenic effects of genotoxic and carcinogenic drugs directly in humans.
- The results of the research will be published in a peer-reviewed journal upon completion of the clinical protocol and a complementary rat study with cyclophosphamide.

[6] Genotoxic hazards are the negative side effects of drugs that could cause gene mutation, which can lead to the development of cancer.

Universal Regulatory Science Strategy for Neurotoxicity Testing

— to assess new materials used in medical devices with neural tissue contact

Evaluating the toxicity of medical devices that come in contact with neural tissue poses challenges for reasons related to the unique vulnerabilities of the nervous system, our limited capacity to repair damage, and differences in devices. Current methods for evaluating neurotoxicity mainly rely on neuropathological and neurobehavioral factors. However, these approaches include a wide variety of methods and endpoints that can be difficult to interpret, and the broad variety of available test methods makes selecting an appropriate testing strategy challenging. Consequently, the medical device industry and FDA have been unable to reach consensus on what constitutes an appropriate level of preclinical neurotoxicity testing for devices that contact neural tissue or cerebral spinal fluid.

To address these issues, in 2008 FDA's Center for Devices and Radiological Health launched a project aimed at defining neurotoxicity and biocompatibility testing standards for the medical device industry and FDA review staff. Once established, these standards will help streamline the preclinical review process of neurological device marketing submissions by reducing the number of FDA requests for additional information and testing. The project has both short- and long-term goals.

2009 Achievements

FDA

- Performed a thorough review of current preclinical testing strategies, neurotoxicity literature, and available guidances and standards
- Held a public workshop in May 2010 with a panel of experts invited to discuss neurotoxicity testing of medical devices and gather public input about possible standards
- Drafted a concept paper on neurotoxicity testing for medical devices that contact neural tissue or cerebral spinal fluid
- Began collaboration to revise ASTM standard F748-06, including writing implantation test methods for inclusion in ASTM standard for medical devices that contact neural tissue

2010 Goals

- Transform the concept paper into a draft guidance and issue it for comment
- Continue work on ASTM standard F748-06

Tools to Detect Adenovirus Vector Toxicity — *It is critical that FDA understand how reliable preclinical studies are for predicting toxicity in humans*

Adenovirus vectors have become a promising new technology in cancer treatment. Approximately 80 investigational clinical trials in the United States are using them, mainly to treat late-stage cancer. Unfortunately, adenovirus vectors can be toxic, preventing them from always being administered at the high doses required to reach tumors in all areas of the body.

Before they are used in humans during clinical trials, drugs are tested for their safety both in animals and using in vitro assays (i.e., not in a living organism). Previous in vitro studies showed that adenovirus vectors activate the complement system (one of the body's early-warning systems for pathogens), but this had never been directly measured in animal studies.

In collaboration with Minnesota's Mayo Clinic, FDA launched a research project in 2007 to identify biomarkers to measure the toxicity of adenovirus vectors in in vitro cell-based assays and animal models and to develop strategies to reduce toxicity. Findings from this project, which are publicly available,[7] are aiding FDA as it reviews investigational applications and will help make clinical trials safer.

2009 Achievements

This research has led to a practical biomarker for studying adenovirus vector toxicity and has also deepened our understanding of the mechanisms of toxicity.

Specifically, the studies have led to two significant health outcomes:

- Identified a practical biomarker — a protein known as C3a — to measure toxicity. This biomarker can easily be adapted for use in humans.
- Discovered that the mechanism for complement activation in animal studies is completely different from the mechanism of complement activation in in vivo studies. This means that widely used in vitro techniques for measuring complement are misleading and, unfortunately, cannot be used as a substitute for animal studies.

[7] Tian, J, Xu, Z, Smith, J.S. et al., Adenovirus Activates Complement by Distinctly Different Mechanisms, in Vitro and in Vivo: Indirect Complement Activation by Virions in Vivo, *Journal of Virology*, Vol. 83, No. 11 p. 5648–5658, American Society for Microbiology, June 2009.

Human Detector Cell Lines to Detect Toxicity in Vaccine Adjuvant Therapy — *to facilitate efficient, cost-effective creation of safe, new vaccine adjuvant therapies and delivery systems*

Vaccine adjuvant therapies are designed to strengthen immunity against pathogens like pandemic influenza, HIV, TB, and malaria. (A vaccine adjuvant is a substance added to a vaccine to make the vaccine more effective.) Many of these adjuvant therapies are at various stages of development and testing. However, some contain components that may lead to unacceptable toxicity — including fever and other negative systemic side effects — in vaccine recipients. Due to the nature of the adjuvants and their mode of action, traditional preclinical toxicity studies in small animals may not be informative or predictive of human safety. It is imperative that developers identify toxicity issues as early in the development process as possible to avoid the waste of time and resources that accompany later product failures.

In January 2008, FDA began working with a sizable group of industry collaborators to create rapid, in vitro (human cell-based) screening assays (test systems) to identify and evaluate potentially toxic activity of new adjuvants and adjuvant delivery systems. FDA is also helping to identify parameters that are predictive of unacceptable toxicities in humans. It is crucial that Agency scientists understand and feel confident that these preclinical studies are reliable.

2009 Achievements

- In 2009, two sensitive human cell lines were identified that can differentiate between *safe* and *unsafe* products and/or doses of novel adjuvants

This effort, which is scheduled for completion in 2010, has additional goals:

- Establish the sensitivity and specificity of pro-inflammatory substances generated in tissue culture of human *detector cell lines* following activation by different classes of adjuvants and delivery systems
- Establish the toxicity threshold for novel adjuvants through studies correlating the in vitro dose responses with adverse reactions in rabbit models
- Evaluate additional human cells for biomarkers predictive of toxicities including neurotoxicity
- Finalize protocols for the safety evaluation assays with the human detector cell lines and make them available to the public

New Tools to Detect Poor Quality, Counterfeit, or Adulterated Drugs — *identify and evaluate rapid screening tests for pharmaceutical ingredients and products in transit*

FDA is working to improve the efficiency of its drug surveillance programs to enable increased testing of in-transit drug articles. The goal is to identify possible counterfeit, contaminated, mislabeled, or otherwise poor quality drugs before they reach consumers. FDA envisions the use of portable spectrometers at various locations, including points of entry, distribution centers, pharmaceutical manufacturer locations, and pharmacies. This project has identified four portable instruments that could be used by FDA field personnel:

- Raman spectroscopy coupled with chemometric methods of data analysis
- Near infrared spectroscopy coupled with chemometric methods of data analysis
- X-ray fluorescence spectroscopy
- Ion mobility spectrometry

2009 Achievements

- Five instruments of each type were purchased with Critical Path funds; they arrived at the Division of Pharmaceutical Analysis lab during the first quarter of FY09.
- Methods for 10 materials were developed on four different types of instruments.
- Studies were performed in collaboration with 5 ORA field labs (New York, Philadelphia, Atlanta, Detroit, and Irvine) to validate the methods that were developed.

In total, 8 collaborative studies were completed to validate the following methods:

- Raman analysis of diethylene glycol contamination of glycerin
- Raman analysis of ethylene glycol contamination of sorbitol
- Near infrared analysis of diethylene glycol in propylene glycol
- Near infrared analysis of melamine in lactose
- X-ray fluorescence analysis of toxic metals in tablets
- X-ray fluorescence analysis of residual catalysts in capsules
- Ion mobility spectrometric analysis of sibutramine in dietary supplements
- Ion mobility spectrometric analysis of fluoxetine in dietary supplements

2010 and Beyond

The collaborative studies were completed successfully by the first quarter of FY2010. Since then, project emphasis has been the instruments' field deployment in a pilot study, being planned in collaboration with ORA Division

of Field Sciences and CDER Office of Compliance. The pilot will include the instruments' deployment to the field and field assignments for pharmaceutical materials analysis. The first method to be deployed will be X-ray fluorescence analysis of imported ayurvedic drug products and substances. All instruments are expected to be deployed by the end of FY2010.

New Tools to Improve the Safety and Effectiveness of Cardiovascular Devices — *leveraging revolutionary research in simulation-based engineering and medical imaging technologies*

To facilitate the efficient development and evaluation of safe, new cardiovascular devices (e.g., implanted stents, vascular grafts, and heart valves) as more people undergo treatment, we must gain a better understanding of the safety and performance of these devices throughout their entire life cycle. Launched in March 2008, this project [8] aims to

- Improve understanding of device performance in critical areas
- Improve the efficiency of FDA's premarket regulatory review process
- Maximize understanding of the total life cycle of cardiovascular devices

Computer simulation methods can manage and integrate data from a variety of sources (animal, preclinical, and clinical) to improve our understanding of device performance and develop standards for product development and evaluation. Through extensive outreach and partnerships with researchers from academia, industry, and the government, this project is developing collaborative projects that use medical imaging and computational modeling techniques to collect relevant data on anatomic and physiologic parameters to cardiovascular device design and performance. One goal is to create publicly available databases of reference data that can be used to develop boundary conditions, as well as reference computer models that should help speed the creation and evaluation of these life-saving devices.

2009 Achievements

- Held a June 1-2, 2009, FDA/ NHLBI/ NSF public workshop on computer methods for cardiovascular devices[9]
- Launched collaborations with researchers to remove barriers to implementing computational modeling, specifically to collect key anatomic and physiologic data and develop computer models
  - — Dartmouth College and m2S: Aortic aneurysm anatomy
  - — Cleveland Clinic Foundation: Superficial femoral artery stenting
  - — Georgia Institute of Technology and University of Pennsylvania: Mitral annular forces
  - — University of Colorado: Coronary artery bifurcation and interatrial septum modeling

[8] For more information about this project, see the following FDA Web page http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm111141.htm.
[9] See: http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm135284.htm).

Electronic Postmarket Safety Monitoring — *Develop and implement a nationwide electronic system (Sentinel System), revolutionizing the way FDA monitors and evaluates its regulated medical products once they reach the market*

Monitoring the safety of its regulated products is fundamental to FDA's mission of protecting public health. Until recently, medical product safety surveillance largely depended on healthcare practitioners and consumers *voluntarily* reporting a medical product's adverse events to the FDA and industry (spontaneous reporting). Today, rapidly evolving technologies are enabling FDA to play a proactive role in monitoring the safety of the products it regulates, enhancing public health safety in ways previously unachievable.

Launched by FDA in May 2008, the Sentinel Initiative is building a national electronic system that will transform the Agency's ability to evaluate the safety of drugs, biologics, and medical devices once they reach the market. The system offers promise as a national resource for safety surveillance. The Sentinel System will enable *active* querying of automated healthcare databases — like electronic health record systems and insurance claims databases — to rapidly and securely evaluate medical product safety issues.[10]

As the system is envisioned, directly identifiable health information would remain in its local environment and continue to be maintained by its owners, who would run requested queries behind existing firewalls and convey only summary results to FDA for review. Once Sentinel is operational, it will help us better evaluate questions about FDA-regulated medical products — enhancing FDA's tools for protecting public health.

2009 Achievements

In 2009, the Sentinel Initiative made considerable strides in laying the System's groundwork.

- FDA received reports on scientific operations, data and infrastructure, governance, and stakeholder outreach and privacy — components critical to Sentinel's development — from seven of the eight contracts it awarded in 2008.
- FDA granted a cooperative agreement to the Brookings Institution to convene public meetings that are essential to gathering broad stakeholder contribution on topics related to systems that actively monitor medical product safety.

[10] Section 905 of the Food and Drug Administration Amendments Act (FDAAA) of 2007 requires FDA to collaborate with public, academic, and private entities to develop methods to obtain access to disparate sources of data and validated methods to link and analyze safety data from multiple sources. FDAAA sets goals for FDA being able to access data from 25 million patients by July 2010, and 100 million patients by July 2012 (Section 905(a), adds new FDC Section 505(k)(3)(B)(i),(ii)(I)-(II)).

- FDA launched a Sentinel Initiative Web page, leveraging Web 2.0 technology to improve communication, ensure transparency, and enlarge opportunities to obtain public feedback.

Moreover, four key pilots recently launched or underway are playing a pivotal role in informing Sentinel's foundation. The Mini-Sentinel pilot, Federal Partners Collaboration, Observational Medical Outcomes Partnership, and SafeRx project with the Centers for Medicare & Medicaid Services are offering valuable insights into the methodology and information infrastructure required to shape the way the Sentinel System is ultimately developed.

- ***Mini-Sentinel*:** In 2009, FDA awarded a contract to Harvard Pilgrim Health Care, Inc., to pilot a miniature Sentinel System (Mini-Sentinel). As part of the project, Harvard Pilgrim will create and pilot a coordinating center that will establish relationships with data partners (e.g., health insurers, healthcare systems), develop scientific methodologies for evaluating postmarket safety issues in near real-time, and ensure data quality. More than 25 organizations are participating in this collaboration. Mini-Sentinel will use a centralized analytical approach, with participants using a common data model to transform their data to a standardized format so that centrally written analytic code can be run in all data partners' databases. To protect personally identifiable information, participating data partners will send only summary results to the coordinating center.
- ***Federal Partners Collaboration (FPC)*:** FPC was built on existing pilots and expanded to include multiple Federal partners (e.g., CMS, Veterans Administration, and Department of Defense). FPC is creating a distributed system focused on testing signal strengthening methodologies (a process that targets a particular medical product and an adverse event of concern to further evaluate whether a correlation really exists between exposure to the product and the particular outcome). FPC gives FDA the chance to observe what happens when a query is implemented with distributed data partners, who each develop their own analytical code based on a common protocol. The lessons learned from this pilot will be compared to those in similar projects, like the Mini-Sentinel (which uses a common data model with centralized analytics), helping FDA to better understand the pros and cons of the centralized versus decentralized analytic approaches.
- ***SafeRx*:** SafeRx was begun by FDA and CMS with initial support from the HHS Assistant Secretary for Planning and Evaluation (ASPE) to incorporate Medicare Part D data for medical product surveillance into ongoing FDA-CMS collaborations that were using Medicare Parts A and B data. SafeRx, which now includes projects in each of FDA's medical product centers, is expanding FDA's capacity to evaluate postmarket product safety and performance, using information about exposure to medical products and their outcomes in the Medicare and Medicaid databases. Along with other ongoing projects, the collaboration is making near real-time safety monitoring of seasonal and H1N1 influenza vaccines possible.
- ***Observational Medical Outcomes Partnership (OMOP)*:** OMOP is a public–private partnership funded and managed through the Foundation for

the National Institutes of Health and chaired by FDA.[11] OMOP is conducting a two-year initiative to develop and test methods for analyzing existing healthcare data to identify and evaluate safety and benefit issues of drugs already on the market and for determining how analyses can contribute to decision-making.

[11] OMOP has 10 Executive Board members, 21 Advisory Board members, and is led by five research investigators and PMO. See OMOP's Web site: http://omop.fnih.org.

New Biomarkers to Help Treat Breast Cancer — *to predict who is initially resistant to trastuzumab, a treatment that improves outcomes for women with HER2-positive breast cancers, and identify women who experience acquired resistance*

Treatment with trastuzumab (also known as Herceptin) significantly improves outcomes for women with human epidermal growth factor receptor 2 (HER2)-positive breast cancer, but it doesn't work in everyone; and tumors can eventually become resistant. HER2 is frequently identified in breast cancer. In 25 to 30% of invasive breast cancers, HER2 is present in sizable amounts, and its presence is associated with aggressive tumors and poor prognosis. In about two-thirds of the women with HER2-positive breast cancers, the tumors are resistant at initial treatment. And many breast cancer patients who respond initially to trastuzumab treatment begin to show resistance within one year (acquired resistance). Researchers do not understand the mechanisms contributing to trastuzumab-resistance and loss of clinical effectiveness.

FDA has been working to identify biomarkers that can predict who is resistant to trastuzumab and who might experience acquired resistance and identify new drugs that can be used to treat trastuzumab-resistant disease.

Achievements in 2009

- FDA found that when Rac1, an important cell signaling regulator gene, is *turned up* to produce more Rac1 protein activity, it causes trastuzumab-resistance.
- FDA also found that trastuzumab-resistance was reversed when trastuzumab-resistant cells were treated with trastuzumab ***and*** the Rac1-specific inhibitor, NSC23766. This indicates that Rac1 may be a potential therapeutic target for treating trastuzumab-resistant disease.
- FDA researchers have shared findings with the research community and the public through publications in a peer-reviewed journal,[12] presentations at research conferences, and press releases.[13]

[12] Dokmanovic M, Hirsch DS, Shen Y, Wu WJ. Rac1 contributes to trastuzumab resistance of breast cancer cells: Rac1 as a potential therapeutic target for the treatment of trastuzumab-resistant breast cancer. *Mol Cancer Ther.* 2009, 8(6): 1557-69.

[13] See press release: AllBusiness.com. http://www.allbusiness.com/pharmaceuticals biotechnology/pharmaceutical/12661668-1.html; See also recent findings from Food and Drug Administration highlight research in breast cancer. Cancer Weekly, August 18, 2009.

Additional Goals

Additional long-term project goals include continuing current efforts to develop new therapeutic products to treat human breast cancers. Specific activities encompass the following:

- FDA researchers are pursuing new ways to increase the magnitude and duration of the response to the trastuzumab treatment.
- Research will continue that suggests that other molecules (IGFBP2 and 3) may serve as biomarkers for determining therapeutic response, as well as resistance to trastuzumab.
- FDA hopes to use proteomic[14] technology and other techniques to investigate the molecular mechanisms of trastuzumab-resistance by establishing the gene expression profiles of trastuzumab-resistant breast cancer cells, as compared to trastuzumab-sensitive cells.

[14] Proteomics is a term that refers to all the proteins expressed by a genome; proteomics involves identifying proteins in the body and determining their role in physiological and patho-physiological functions.

ArrayTrack™, FDA's Genomic Tool — *to develop and refine ArrayTrack to advance the use of pharmacogenomic data in developing and evaluating medicines*

The world of pharmacogenomics — the study of how an individual's genetic inheritance affects the body's response to drugs — has confirmed that the old adage "one man's meat is another man's poison" can apply equally to medicine. A drug that may be effective for one person may not only be less effective for another, it may be downright harmful — even at the same dose.

Increasingly, new pharmacogenomics technologies are being used during medical product development, providing critical information about who will respond to a specific therapy and who may not respond (or who could actually be harmed). These types of data will help to individualize treatments, making them safer and more effective. However, pharmacogenomics research generates a tremendous amount of complex data — a challenge for FDA's regulatory review teams. In 2004, as part of FDA's Voluntary Genomic Data Submission program, the Agency began encouraging sponsors to submit their pharmacogenomic data to FDA to facilitate our ability to receive, understand, and review this new type of data.

ArrayTrack is the key bioinformatics tool being used in the voluntary genomic data submissions program to receive and analyze the data. Originally, ArrayTrack could only receive DNA microarray data. In 2008, FDA launched an effort to update and refine ArrayTrack to enable it to receive, analyze, and manage the review of pharmacogenomics data beyond microarrays, including proteomics,[15] metabolomics,[16] and, most recently, genome-wide association study data. A series of new modules are in development that will make ArrayTrack more efficient, enabling the Agency to more proficiently review and analyze all of the genomic data it receives.

2009 Achievements

- Developed a module to handle data from genome-wide association studies

2010–2011 Goals

- Plan to have developed additional modules to handle proteomics and metabolomics data by the end of 2011.

[15] The branch of genetics that studies the full set of proteins encoded by a genome
[16] The systematic study of the unique chemical fingerprints that specific cellular processes leave behind

Personal Genomic Information to Diagnose and Predict Outcome

— *Develop community-wide consensus on best practices for developing and validating microarray-based classification models. This is a step towards achieving the enormous potential of personalizing treatments by reliably predicting diagnosis, prognosis, and treatment outcomes using a patient's personal genomic information*

Microarray technologies are used widely in basic and clinical research, including for identifying biomarkers of drug efficacy and safety. (A microarray is a sequence of microscopic dots of DNA, protein, or tissue arranged on a glass, plastic, or silicon chip for simultaneous analysis. The most well-known is the DNA microarray, which plays a key role in gene expression profiling. Other names for the DNA microarray are gene chip, DNA chip, and biochip).

To fully translate these technologies for use in the clinic, standards and quality measures must be devised and implemented. Initiated by FDA in collaboration with about 200 participants from academia, industry, and government, the MicroArray Quality Control (MAQC) project encourages the application of microarrays in discovery, development, and review of FDA-regulated products.

Phase 1 of the project (MAQC-I) demonstrated the technical reliability of microarray technology in terms of identifying differentially expressed genes. Phase 2 (MAQC-II) assessed the capabilities and limitations of various data analysis methods in developing and validating microarray-based classification models for predicting patient outcomes, thus providing a solid scientific foundation for our ability to personalize medicine.

2009 Achievements

During 2009, substantial progress has been made. Key achievements include:

- Generated large training and validation sets of microarray gene expression and genotyping data, using tissue samples from cancer patients whose clinical outcomes are well annotated
- Investigated the impact of various modeling factors on the performance of classification models
- Recommended standard operating procedures (SOPs) for the clinical and scientific communities for generating classification models to predict patient outcomes
- Summarized major findings in multiple manuscripts that are currently under peer review

2010 Goal

FDA is planning a public meeting for the second half of 2010 to communicate MAQC-II findings to the public and to work on a guidance for industry and FDA reviewers that will help translate our research results for application in the clinic.

Greater Use of Pharmacogenomic Data in Product Development

Pharmacogenomics is the study of how variations in a person's genetic makeup (all of the hereditary material an organism possesses) affect the person's response to medications. The use of genomic information, accelerated by the sequencing of the human genome and the emergence of new tools and technologies, has paved the way for enormous opportunities in drug discovery, development, and use.

As part of its mission to promote and protect public health, FDA has become a strong proponent of pharmacogenomics, spurring an innovation process that is making medical products safer and more effective. In September 1998, the Agency approved the original application for trastuzumab (Herceptin to treat breast cancer), advising on the label that the medication be used in a particular patient subpopulation to which the beneficial effects of the drug are largely limited. (See write up on trastuzumab.)

In the decade that followed, the Herceptin example has served as a model for the subsequent development and regulatory review of personalized treatments. Treatments include the blood-thinner warfarin (Coumadin), whose label was first updated in 2007, based on a combination genotype related to the drug's pharmacokinetics and pharmacodynamics as well as the medication carbamazepine (Tegretol, Tegretol XR, Equetro, Carbatrol), whose label indicates a strong link between a serious side effect called Stevens-Johnson syndrome[17] and a gene variant found almost exclusively in patients with Southeast Asian ancestry.

Recognizing that certain hurdles remain to translating pharmacogenetic research into clinical practice, FDA has initiated a number of leading-edge infrastructure projects, including a training program in genomics for all stakeholders (FDA staff, academia, industry) to apply our knowledge of the human genome to the development and clinical translation of personalized therapies that can treat today's biggest killers.

In 2004, FDA launched the ***Voluntary Genomic Data Submissions*** program (VGDS) to enable pharmaceutical companies, consortia, academia, and individuals to partake in a scientific exchange with the Agency and to allow FDA regulatory scientists to acquire experience with data in this burgeoning field. This program later was renamed the Voluntary Exploratory Data Submissions (VXDS) program to reflect the wide diversity of biomarkers applied in drug development and clinical practice.

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[17] Stevens-Johnson syndrome is a rare, serious disorder in which your skin and mucous membranes react severely to a medication or infection. Often, Stevens-Johnson syndrome begins with flu-like symptoms, followed by a painful red or purplish rash that spreads and blisters, eventually causing the top layer of your skin to die and shed. See http://www.mayoclinic.com/health/stevens-johnson-syndrome/DS00940.

What began as a voluntary pilot project to encourage sponsors to submit genomic data for Agency evaluation and education has transitioned to more routine submissions of pharmacogenomic and applied biomarker data in regulatory submissions (i.e., NDAs and BLAs), as well as increased consultation with FDA about biomarker development plans in investigational planning stages. The Office of Clinical Pharmacology's Genomics Group has seen a growth of greater than 250% in therapeutic product review of pharmacogenetic and biomarker data between 2008 and 2009 alone.

FDA is committed to aligning its regulatory science policies with advances in genomics and personalized medicine. A short-term goal is to develop and issue guidance for industry to encourage the use of genomics in drug development.

2009 Program Achievements

- Developed CDER Genomics Group review infrastructure and best practices
- Increased regulatory review productivity by over 250%
- Improved risk–benefit balance of approved drugs by including pharmacogenetic labeling language for the drugs clopidogrel (Plavix), panitumumab (Vectibix), Cetuximab (Erbitux)
- Established working groups for developing guidance
- Facilitated 5 VXDS meetings between sponsors and FDA

2010 Goals

- Continue improving risk–benefit balance of approved drugs by enhancing drug product label language to include pharmacogenetics, where appropriate
- Enhance biomarker science through policy development and engagement of FDA and external communities
- Issue draft guidances on
    - Clinical pharmacogenomics in early drug development
    - Enrichment strategies in clinical trials
- Expand VXDS program to include academic researchers and other stakeholders

New HIV Tests to Measure Emerging Variant HIV Strains — *to secure the nation's blood supply as well as diagnose and manage patients effectively*

HIV mutates over the course of an affected person's lifetime to a more lethal form of the virus that eventually leads to full-blown AIDS. New forms of HIV continue to emerge worldwide, particularly in Africa. Although HIV subtype B is the predominant strain in the United States, the percentage of emerging variants has risen, constituting about 5% in the blood donor population and 20% in the public health setting. A persistent effort to detect major new variants and subtypes is critical to ensuring the safety of the nation's blood supply and diagnosing and managing patients effectively. When reviewing marketing applications for new drugs and diagnostics, FDA must be able to depend on the validity of tests that were used during development.

In May 2006, FDA began conducting studies in rural and urban Cameroon, where the first HIV strains were shown to have emerged and numerous diverse strains have emerged since. This research is enabling FDA to access these strains and to develop new tools (e.g., reference panels) that can be used to evaluate the effectiveness of tests that are used during diagnostic and drug development. FDA is working with New York University to characterize the HIV strains being identified in Cameroon to create a repository of well-defined reference materials (i.e., virus strains). These virus strains will be used to support drug and diagnostic development to help ensure blood safety and the effectiveness of new vaccines and therapies.

2009 Achievements

During 2009, two key efforts advanced:

- Tools were successfully developed to detect the nucleic acid of two recently emerged, predominant HIV variants (CRF 02_AG and CRF01_AE) that could not be reliably detected using existing tests
- A study of virus tropism (virus ability to infect certain body cell types), transmissibility, and pathogenesis of these new strains was launched that will continue as part of future goals

2010 Goals

- Develop tools (reference panels) for HIV protein and nucleic acid detection for two additional emerging strains
- Continue the study on tropism
- Continue in global collaborations (NIH, CDC, WHO, the HIV community and blood organizations) to expand reference materials and make information available on diagnostics and virus characteristics in early and late disease stages to the HIV scientific community. This information will be important to developing effective new diagnostics, therapies, and vaccines.

Better Investigation of Contamination Outbreaks — *using microarray technology to investigate antimicrobial resistance in Salmonella*

Antimicrobial resistance is a global public health challenge. FDA is particularly concerned with the development and spread of resistant pathogens in the food supply and the genetic mechanisms underlying these resistances. The Agency is using microarray technology to investigate antimicrobial resistance in *Salmonella* to understand pathogen evolution and aid in contamination outbreak investigations.

Microarray technology uses a glass slide that is imprinted with hundreds of thousands of unique DNA probes. These *gene chips* are a powerful tool for rapidly determining the genomic repertoire of a particular organism. They enable the individual genetic features contained within a particular bacterial genome to be identified and detected. The recent explosion of whole genome sequencing data has allowed the construction of microarrays that represent many different species, on a single glass slide.

FDA is using custom DNA microarrays, representing four different species of food-borne pathogens, as a means of understanding the genomic complexity and evolution of enteric pathogens. This research will aid in outbreak investigations and increase our understanding of how these bacteria cause disease or resist antibiotic treatment.

One of FDA's goals has been to understand the temporal relationship between the approval of antimicrobial drugs and the appearance of specific antimicrobial resistance determinants. To do this, we must gain insight into the consequences of antibiotic use and the means bacteria employ to survive antimicrobial exposure. This information will improve risk management strategies, aid in antimicrobial product regulation, and help public health officials formulate sound, science-based policies.

2009 Achievements

- Using microarray technology, FDA characterized approximately 81 strains from a historical collection of *Salmonella enterica* serotype Typhimurium, one of the most prevalent food-borne pathogens.
- Preliminary results identified various antimicrobial resistant genes (in this pathogen) that have emerged during the past six decades and demonstrated the importance of mobile genetic elements in the emergence of resistance.

Goals Planned for 2010

- Use comprehensive microarray technology to characterize a collection of 120 isolates of *Salmonella* Typhimurium collected over the past 6 decades
- Identify and categorize the genetic factors contributing to the emergence of resistance and correlate with the time when corresponding antibiotics were approved for use in human and veterinary medicine
- Correlate antibiotic resistance profiles with the genomic make up of this pathogen group
- Describe the overall genomic diversity of this pathogen group as a function of time and geography

Safety of Anesthetics and Sedatives in Young Children — *to improve the safety of anesthetic and sedative use in young children*

Millions of children receive anesthesia each year. Studies in juvenile animal models show exposure to some anesthetics and sedatives to be associated with memory and learning deficits and other neurodegenerative changes in the central nervous system. Insufficient human data exist to support or refute the possibility that similar effects could occur in children.

To address this issue, FDA is partnering with multiple stakeholders — professional anesthesiology societies, academic research institutions, patient advocacy groups, industry, and other government and nonprofit organizations — to launch the Safety of Key Inhaled and Intravenous Drugs in Pediatrics (SAFEKIDS) Initiative, a multi-year effort to tackle major gaps in scientific information concerning the safe use of anesthetics and sedatives on children. FDA has awarded five contracts under the auspices of the SAFEKIDS Initiative.

2009 Achievements

- Launch the initiative (framework for six key studies)

Studies/Participants

- The ***International Anesthesia Research Society*** (IARS) is charged with leading the administrative oversight and overarching framework for the SAFEKIDS Initiative public-private partnership (PPP) to support the scientific studies as well as assess and develop additional studies over time
- ***Children's Hospital Boston*** – Harvard University is conducting a long-term study with neurodevelopmental outcomes in pediatric patients who are given local or general anesthesia as neonates or infants
- ***Arkansas Children's Hospital Research Institute*** – will conduct a study assessing neurocognitive, emotional, and behavioral outcomes in a group of toddlers and children exposed to anesthesia as infants during cardiac surgery
- ***Columbia University*** – will evaluate the effects of anesthetic exposure on neurocognitive, emotional, and behavioral outcomes in pediatric patients as compared to their unexposed siblings
- ***Mayo Clinic*** – will use an extensive epidemiologic database to study long-term cognitive development following exposure to general anesthesia during infancy
- FDA's ***National Center for Toxicological Research*** – began studies in non-human primates to assess decline in mental function in young animals exposed to anesthesia; NCTR will also develop noninvasive ways of using imaging to measure structural changes in the brain

2010 – 2012 Goals

- Analyze and publish the results of these studies to inform risk–benefit decisions that both anesthesiologists and parents must make when considering the choice of anesthesia in pediatric patients.

FDA expects the first results from the SAFEKIDS Initiative to be available in late 2010.

The Clinical Investigator Training Course — *to increase the cadre of well-trained, experienced clinical investigators, improving the quality of clinical research*

Clinical investigators play a pivotal role in medical product development by providing FDA with the clinical data for regulatory decisions. Yet, the clinical trial industry faces a chronic shortage of well-trained, experienced clinical investigators committed to performing clinical trials over the long haul.

The resultant need to continually recruit new investigators drains valuable resources and may 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 also may not fully apprehend FDA's regulatory and monitoring requirements.

To help develop a cadre of well-trained investigators, FDA's Critical Path Initiative launched in 2009 a Clinical Investigator Training Course to be held annually, targeted at medical professionals (experts who sign FDA Form 1572 before participating in an investigation). The 3-day course includes lectures given by senior FDA experts and guest lecturers from industry and academia, providing FDA's perspectives on new safety concerns, adverse event monitoring, compliance with legal and ethical obligations of clinical research, and acceptable scientific and analytic standards in clinical study design and conduct.

The first annual course, held November 16, 17, and 18, 2009, quickly filled to capacity, drawing 125 participants from across the United States and from as far away as Japan, Mali, Egypt, and Taiwan. The next course, which will be video-streamed and available to the public on the Critical Path Web site, is tentatively scheduled for November 8, 9, and 10, 2010.