Critical Path Initiative

Report on Projects Receiving Critical Path Support

Fiscal Year 2010 Report (October 1, 2009 – September 30, 2010)

In Response to Senate Report 111-039

Food and Drug Administration

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Commissioner of Food and Drugs

Introduction

Senate Report 111-039 contains the following request:

> *Critical Path and Modernizing Drug Safety.—The Committee recommendation includes $18,000,000 for the critical path initiative, including not less than $6,000,000 for critical path partnerships, as authorized by section 566 of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The Committee expects that this funding will be used to further FDA's work on critical path opportunities and to promote collaborations with other government agencies, academia, patient groups, and other interested parties including, but not limited to, the Critical Path Institute, the National Institute for Pharmaceutical Technology and Education, the Coalition Against Major Diseases, and the Coalition Against Tuberculosis.*
>
> *Of the $6,000,000 provided for critical path partnerships, not less than $2,000,000 shall be used to support research partnerships for the treatment and/or rapid diagnosis of tropical diseases as defined by section 524 of the FD&C Act. The Committee is particularly concerned with treatments for tuberculosis (TB) and drug-resistant TB. Worldwide, almost 2 million people die from TB and more than 9 million people develop active disease every year. The rise of drug-resistant TB can result in a global, untreatable epidemic. The Committee believes that the use of single drugs too often results in drug resistance and that more effective combinations of treatment are needed. Therefore, the Committee directs the Center for Drug Evaluation and Research to enter into a competitive agreement with an entity eligible for funding under section 566 of the FD&C Act to assist with the development of new combinations of drugs for the rapid and effective therapy of tuberculosis.*
>
> *The Committee directs FDA to report on critical path spending quarterly. Reports should include activities undertaken with the $18,000,000 provided for the overall initiative and more specifically projects awarded with the $6,000,000 in partnership funding. The report shall include the amount of each project or activity, the center responsible for the funding, a description of the specific project or activity being funded, and in the case of partnership funding, the recipient of the funds.*

The Food and Drug Administration (FDA) has prepared the following report in response to the Committee request. This is a report of projects supported by the Critical Path Initiative (CPI) and covers fiscal year (FY) 2010, October 1, 2009 – September 30, 2010. The report includes data from centers receiving CPI funding.

CPI Background

CPI is FDA's national strategy for transforming the way FDA-regulated products – especially human drug and biological products, medical devices, and veterinary drugs – are developed, evaluated, and manufactured. With collaboration as its cornerstone and following extensive input from FDA experts and the public, CPI identified broad areas of Critical Path focus in its 2006 report including:

- developing better evaluation tools, such as biomarkers and new assays
- streamlining clinical trials by modernizing the clinical trial sciences to make trials safer and more efficient

- harnessing bioinformatics and moving FDA from a paper-based to an electronic environment for exchanging data and safety surveillance
- moving manufacturing into the 21st Century, using tools such as process analytic technology and nanotechnology
- developing products to address urgent public health needs, including, for example, improved antimicrobial testing, new animal models to test bioterrorism countermeasures, and vaccine testing
- focusing on at-risk populations, such as pediatrics.

In March 2004, FDA launched the CPI with the landmark report *Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products.*[1] This report was prompted by the severe decline in the number of innovative medical products submitted for approval, despite advances in biomedical sciences. The report noted:

- the rising cost, difficulty, and unpredictability of product development
- the use of outdated scientific tools of the past century and, thus, the need to transform the sciences of medical product development including new in vitro tests and assays, computer modeling, qualified biomarkers, and innovative trial designs.

FDA opened a public docket to collect the views of all stakeholders on the most pressing scientific hurdles in product development. Based on what was learned from the public and through FDA scientists' unique perspectives, FDA identified areas of greatest opportunity for improving product development science and translating those improvements into public health benefits. Outreach results were published in the *Critical Path Report and Opportunities List* in March 2006. The report listed 76 specific activities organized into six key areas, which, if carried out, could dramatically improve product development.[2] With existing resources, FDA created the Office of Critical Path Programs to help move this work forward.

In 2006 and 2007, FDA documented Critical Path achievements on its Web site listing CPI-related activities either launched by FDA or with FDA participation.[3] Projects were tracked based on the 76 specific activities identified in the 2006 Opportunities Report and List. A 2008 report, issued in early spring 2009, highlighted only those CPI projects that received funding during 2008 — an informal survey that revealed CPI collaborations involving 84 government agencies, universities, industry leaders, and patient groups from 28 states and five countries. In spring 2010, FDA issued a report on 2009 CPI activities, spotlighting 22 of FDA's ongoing CPI research projects.

This current report describes the CPI projects that received funding during FY 2010. Each project is listed, along with relevant collaborators and funding received, and described briefly in the text. Projects are organized by FDA center.

Targeting Public Health Outcomes

Although many of the projects listed in this section are in progress, a number of intermediate outcomes can already be noted. The following are examples of accomplishments of CPI-supported projects since the FDA launched CPI. For more details on individual CPI project

[1] CPI reports are available at www.fda.gov/CriticalPath.
[2] Ibid.
[3] Ibid.

achievements, please see the activity reports for 2006 through 2009 on the OCPP Web site at www.fda.gov/CriticalPath.

Biomarkers/Other Tools to Facilitate Personalize Medicine

- Publicly Available Tools to Build Safer Drugs: New Data on the Genetic Basis of Adverse Drug Events. In early 2010, the ***International Serious Adverse Events Consortium***, a non-profit partnership of 10 international pharmaceutical companies and academic institutions, whose launch CPI facilitated, announced the release to the public of data on the genetics of adverse events – negative side effects – for 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.
- Safer Use of Clopidrogel. For people using ***clopidrogrel*** (Plavix), a drug used to lower the risk of blood clots, the discovery of genetic variations that may render the drug ineffective resulted in the 2009 addition of label dosing information. After more research into the data, in early 2010, FDA highlighted this concern in a boxed warning.
- Early Identification of Kidney Toxicity. ***The Predictive Safety Testing Consortium***, a public–private partnership led by the non-profit organization (the Critical Path Institute, or C-Path) and supported by the CPI, facilitates industry's data sharing to receive, review, and approve new tools as qualified for use in drug development. In May 2008, seven new biomarkers that signal kidney injury were reviewed and qualified. These biomarkers can be analyzed through laboratory tests on urine. These new tests can now be used in laboratory research to detect acute drug-induced kidney toxicity.
- Safer Use of Warfarin. Warfarin has a problematic safety profile in part because it has a narrow therapeutic range, and in part because patients vary greatly in the dose needed for adequate anticoagulation. The consequences of under-dosing and over-dosing are severe — including elevated risk of death from stroke from under-dosing, and bleeding from over-dosing. FDA's Critical Path Initiative funded a research project with the University of Utah and the Critical Path Institute of Tucson, Arizona, to develop genetically based instructions for warfarin (brand name: Coumadin) dosing. The Initiative has also facilitated planning with the National Heart, Lung and Blood Institute for a clinical trial that will study warfarin dosing based on genetic test information and is helping to pay for another clinical study being conducted by Harvard Partners that will derive personalized warfarin dosing algorithms for patients new to the drug. This collaborative research into the genetics of people using warfarin led to the addition of supplementary dosing information to warfarin labels.

Modernizing Clinical Trials

- In February 2010, FDA issued two draft guidances making recommendations on innovative trial designs – adaptive and non-inferiority designs. In adaptive trials, data gathered as the trial progresses are used to change some aspect of the trial midstream. Non-inferiority trials are used to show that the effect of a new treatment is not worse than that of an active control by more than a specified margin.

- Clinical investigators are vital to medical product development because they provide FDA with clinical data that is relevant in making regulatory decisions. The clinical trial industry faces a shortage of well-trained, experienced clinical investigators committed to performing clinical trials for the long haul. As a result, resources are drained as there is a continuous need to recruit new investigators who may not be fully equipped to recognize safety issues, ethical problems, and study design flaws. To help develop a cadre of well-trained investigators, FDA and the Clinical Trials Transformation Initiative (CTTI) sponsored the very first CPI's annual three-day training courses in November 2009 for clinical investigators. The goal of the training courses is to better prepare investigators to safely and effectively perform clinical studies of investigational products. FDA and Duke University launched CTTI, a broad-based collaboration with the goal of modernizing the U.S. clinical trials enterprise, in 2008.

Using Health Information Systems to Improve Safety Evaluation and Surveillance

- In 2010, quicker review of new drugs for chronic hepatitis C became possible through the Anti-viral Information Management System, an Oracle database used by FDA staff to speed the review of hepatitis C protocols. An automated clinical trial simulation module is being developed that will help inform dose selection, and a tool will soon be available to archive and report on completed analyses.

- Monitoring the safety of its regulated products is a major part of FDA's mission to protect public health. The Sentinel System enables FDA to actively query diverse automated healthcare data holders – like electronic health record systems, administrative and insurance claims databases, and registries – to evaluate possible medical product safety issues quickly and securely. In late fiscal year 2009, FDA competed and awarded a contract to Harvard Pilgrim Health to create a pilot program for the Sentinel System (Mini-Sentinel) for electronic monitoring of post-market safety.

- This is a pilot project aimed to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Ongoing cooperative efforts with other federal agencies have expanded to include additional partners, such as the U.S. Department of Veterans Affairs and the Department of Defense, in the Federal Partners pilot to develop active electronic surveillance methods and conduct medical product-adverse outcome queries.

- SafeRx, collaboration among Centers for Medicare and Medicaid Services, FDA, and Assistant Security Planning and Evaluation is up and running, enhancing FDA's existing safety surveillance capacity and providing close to real-time, electronic vaccine safety monitoring of seasonal and H1N1 influenza vaccines.

- Publicly Available Tools to Build Safer Drugs: Reducing Cardiac Toxicity. A collaboration of private- and academic-sector partners and FDA that began in 2007 under the CPI, created the ECG Warehouse, a repository of digital electrocardiograms (ECGs) that is being used to study the cardiac toxicity of drugs. This allows the FDA to electronically search abnormal ECG's and determine if they were linked to a drug.

Responding to Congressional Concerns -- Tropical Diseases, Especially Tuberculosis (TB)

As noted in Senate Report 111-039, there is an urgent need for new treatments for tropical diseases, and in particular for TB. Several of the projects described in this report target those conditions. Anchoring this work are five competitive awards, made through a Request for Application, at the end of September:[4]

- ***Aeras Global TB Vaccine Foundation*** -- for the discovery of biological and immunological biomarkers for TB vaccines
- ***The Global Alliance for TB Drug Development*** -- to develop a repository of clinical trial specimens (the Frozen Trial Initiative) and to qualify new preclinical models for the development of TB drug combinations
- ***The University of Georgia Research Foundation, Inc.*** -- to develop a diagnostic for latent TB
- ***Colorado State University*** -- to qualify small molecule biomarkers of TB treatment, relapse, and cure
- ***The University of Utah*** -- to develop and validate point-of-care tests for TB (ultrasensitive SERS detection technology for low concentration antigens)

Next Steps

Moving forward, the FDA will begin to realign the Critical Path Initiative to coincide and address the scientific priority areas defined in the recently released regulatory science white paper, which outlines the Agency's Advancing Regulatory Science Initiative. A significant portion of the regulatory science initiative is aimed at supporting new science to overcome the hurdles inherent in the current medical product development paradigm. Advances in regulatory science will help modernize product development to provide better tools, standards, assays, disease models, and science-based pathways to improve the efficiency, predictability, capacity, and quality of FDA-regulated products, as well as to support safety surveillance of FDA-regulated products once they reach the market.

Additionally, FDA is engaged in a science strategic planning process, which will further refine agency-wide regulatory science priorities for the next one-to-five years. The Critical Path programs will be reconfigured or developed to address these scientific priority areas concentrating on integrated internal and external collaborative projects to further FDA regulatory science. Thus, subsequent reports will reflect work that is targeted to the agency's top scientific priority areas that advance the scientific challenges of medical product development.

The following *Highlights* illustrate the depth and breadth of the Critical Path Initiative in 2010.

[4] For more on the RFA, see www.fda.gov/CriticalPath.

Highlights of FY 2010 Activities

For fiscal year (FY) 2010, Congress "recommended $18,000,000 for the Critical Path Initiative, including not less than $6,000,000 for critical path partnerships [to] further FDA's work on critical path opportunities and to promote collaborations with other government agencies, academia, patient groups, and other interested parties. . . . "

A variety of Critical Path Initiative (CPI) projects were under way in 2010, often in collaboration with stakeholders. The following is just a sampling, showing the breadth and depth of FDA's CPI work.

Summary

- More than 70 CPI projects received FDA funding support during FY 2010.
- $10,720,065 (of the $18,000,000 total) went to support CPI partnerships.
- $2,934,323 in grants to support six innovative projects on tuberculosis.
- FDA collaborated with more than 35 organizations on CPI projects (including Albert Einstein College of Medicine, Baylor College of Medicine, Feinstein Institute for Medical Research, Cleveland Clinic, University of Pittsburgh, University of Virginia, National University of Singapore, Mayo Clinic, Harvard/Boston Children's Hospital, University of Arkansas, Johns Hopkins University, National Naval Medical Center, National Institutes of Health, IBM, Novartis, SAIC/NCI, GenVac).

Biologics (Vaccine/Blood)

- Seven CPI projects are underway to improve vaccine safety. For example, one of the projects supports the development of a tool for predicting safety and efficacy of a novel substance that increase the ability of vaccines to stimulate protective immune system responses (adjuvant). The data from the project could assist in the selection of safer vaccines for further development and could reduce the use of small animal models.
- Six CPI projects ongoing to promote development of innovative therapies in the area of cancer and regenerative therapies. FDA scientists are working to determine if a protein called Notch2 can be used as a biomarker to support the development of new stem cell-based products for tissue regeneration.
- Nine CPI projects focus on ensuring blood safety. For example, FDA is developing product quality biomarkers for stored blood cells to determine if stored blood can be safely used for transfusion; this would also prepare FDA for future regulatory challenges in the area of blood safety and testing.
- One CPI project is underway to support the development of treatments for allergic diseases.

Drugs and Therapeutic Proteins

- SAFEKIDS is a CPI project to evaluate the safety of inhaled and intravenous anesthetic drugs in children.
- CPI work is being done to assess drug-related cardiac toxicity.
- CPI projects are ongoing to address kidney, liver, and muscle injury, to facilitate development and review of drugs to treat hepatitis C and multiple sclerosis and to stimulate development of new safe and effective pain killers.

- A long-term CPI effort is under way to spur use of modern manufacturing techniques.

Clinical Trial Modernization

- CPI projects are ongoing in FDA Centers that support more efficient clinical trials, including projects to improve the monitoring process and the process for reporting of serious adverse events.
- The second annual clinical investigator course was held on November 8, 9, and 10, 2010.

Device-Related Work

- FDA supported CPI device-related projects in 2010, including projects to assess disk replacement devices, assess blood damage in medical devices, encourage the development of bioabsorbable implants, and facilitate development of pediatric cardiovascular devices.
- CPI work is in progress to develop regulatory approaches for integrating nanotechnologies into medical diagnostic and devices.
- CPI medical imaging and simulation-based technologies are being evaluated for their use in device design and evaluation.
- CPI work is under way in the area of autonomous drug administration devices to improve personalized dosing and safety.
- Scientists are looking at standardizing the use of brain functional Magnetic Resonance Imaging (fMRI) as a biomarker for clinical trials.
- A model is being developed to assess the effect of breast pump use on infant health.

Food Safety

- CPI projects for food safety range from the analysis of *Salmonella enterica*, commonly associated with foodborne outbreaks from fresh-cut product and poultry, to studies of factors that affect the antioxidant activities of dietary supplements, to organism detection relevant to epidemiological studies.
- One CPI project involves working to develop a microarray for the genetic discovery of enteric pathogens and analysis of gastrointestinal issues.

Veterinary Medicine

- FDA is developing regulatory tools to ensure the public health by protecting the food supply with regard to genetically engineered animals.
- FDA has obtained data from a *Salmonella* study that can help with risk-based decision making regarding human and animal use of antimicrobials.
- Work is ongoing to improve methods for controlling unexpected toxic reactions to drugs in dogs; the result will be dramatic decreases in costs to dog owners for veterinary care.

Pharmacogenomic / Toxicology Projects

- ArrayTrack™ is supporting evaluation of complex pharmacogenomic data being submitted to FDA in marketing applications. This effort directly affects regulatory decision making.
- A liver toxicity knowledge base is being developed and maintained to support research into relationships among diseases, genes, proteins, and drugs.

FY 2010 Critical Path Funding Overview and Project Summaries

Table 1: Summary of FY 2010 Critical Path Initiative Obligations

Center	Total 2010 CP Funding	1st Quarter Funding	2nd Quarter Funding	3rd Quarter Funding	4th Quarter Funding	FY Total Funding
Office of Critical Path Programs (OCPP)	$6,604,000	$0	$183,985	$0	$6,420,015	$6,604,000
Center for Biologics Evaluation and Research (CBER)	$1,725,000	$0	$51,460	$581,300	$1,053,690	$1,686,450
Center for Drug Evaluation and Research (CDER)	$3,358,000	$0	$0	$0	$3,358,000	$3,358,000
Center for Devices and Radiological Health (CDRH)	$4,284,000	$0	$166,850	$2,683,079	$1,402,837	$4,252,766
Center for Food Safety and Applied Nutrition (CFSAN)	$500,000	$134,854	$161,825	$167,810	$35,511	$500,000
Center for Veterinary Medicine (CVM)	$500,000	$17,618	$113,190	$266,473	$102,719	$500,000
National Center for Toxicological Research (NCTR)	$1,379,000	$183,979	$337,011	$275,730	$600,094	$1,396,814
Total	**$18,350,000**	**$336,451**	**$1,014,321**	**$3,974,392**	**$12,972,866**	**$18,298,029**

Table 2: Summary of FY 2010 Critical Path Initiative Obligations to Section 566[5] Partnerships

Center	Total 2010 CP Funding	FY Total CPI Spending	Funding to Support Partnerships per §566 of the FD&C Act.
Office of Critical Path Programs (OCPP)	$6,604,000	$6,604,000	$5,932,323
Center for Biologics Evaluation and Research (CBER)	$1,725,000	$1,686,450	$148,000
Center for Drug Evaluation and Research (CDER)	$3,358,000	$3,358,000	$3,014,887
Center for Devices and Radiological Health (CDRH)	$4,284,000	$4,252,766	$1,624,855
Center for Food Safety and Applied Nutrition (CFSAN)	$500,000	$500,000	$0
Center for Veterinary Medicine (CVM)	$500,000	$500,000	$0
National Center for Toxicological Research (NCTR)	$1,379,000	$1,396,814	$0
Total	**$18,350,000**	**$18,298,029**	**$10,720,065**

Critical Path activities in FDA centers and offices are described in more detail in the following pages.

[5] Eligible entities for CPI partnerships include institutions of higher education (as such term is defined in section 1001 of title 20) or a consortium of such institutions; or an organization described in section 501(c)(3) of title 26 and exempt from tax under section 501(a) of such title. The eligible entity must also have experienced personnel and clinical and other technical expertise in the biomedical sciences, which may include graduate training programs in areas relevant to priorities of the Critical Path Initiative. (Section 566 of the FD&C Act [21 USC §360bbb–5] identifies the FDA authority for funding Critical Path Public-Private Partnerships).

Office of Critical Path Programs (OCPP) FY 2010 Summary

Office of Critical Path Programs (OCPP)							
	Project	**Partnerships**	**Q1**	**Q2**	**Q3**	**Q4**	**FY Total Funding**
1	**Clinical trial efforts to modernize the clinical trial enterprise, including improving efficiencies and safety; investigator training**	Clinical Trial Transformation Initiative collaboration co-leaders: FDA-Duke	$0	$0	$0	$1,499,000	$1,499,000
2	**Crititcal Path Insititute Projects (C-Path)**	C-Path	$0	$0	$0	$1,499,000	$1,499,000
3	**Tropical Diseases, especially TB**	Aeras Global TB Vaccine Foundation; Global Alliance for TB Drug Development; The University of Georgia Research Foundation Inc.; Colorado State University; The University of Utah	$0	$23,985	$0	$2,934,323	$2,958,308
4	**Bioinformatics projects**	None identified	$0	$0	$0	$287,692	$287,692
5	**Optimize sampling of laboratory results for premarket safety assessment**	None identified	$0	$160,000	$0	$0	$160,000
6	**Regulatory Science innovations effort**	NIH, University of Michigan	$0	$0	$0	$200,000	$200,000
	Total OCPP Funding		**$0**	**$183,985**	**$0**	**$6,420,015**	**$6,604,000**

OCPP Project Summaries

1. **Clinical Trial Efforts**. Much of the nation's clinical trial enterprise is moving offshore due to the costs of conducting clinical research in the United States. However, American patients could be disadvantaged if medical innovations are primarily studied in non-U.S. populations. For example, data from comparative effectiveness trials in China will be difficult to apply effectively to the U.S. population. The success of the U.S. clinical trial enterprise in our nation will depend on continued public confidence in trial safety, integrity, and transparency. We need to streamline U.S. clinical research practices, while bolstering patient safety. In 2007, these concerns led FDA and Duke University to launch the Clinical Trials Transformation Initiative (CTTI) – a unique public–private partnership bringing together

diverse stakeholders[6] in the clinical trial industry with a mission to identify practices that, 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 projects of the CTTI follows.

- Effective and Efficient Clinical Trial 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 an expert group to integrate results and recommend ways to optimize reporting of SAEs to investigators and ensure subject protection.

- Collaborations

CTTI collaborates with other organizations in educational and research initiatives to improve clinical trials. Collaboration activities include:

  - Use of Clinical Trials to Evaluate 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

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

medical products and procedures if (1) operational efficiency were 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.[7]

– Standards for Collecting Information about 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, MD, attracting participants from around the world. The course takes place in November.[8]

2. **Critical Path Institute Projects (C-Path).** C-Path is an independent, non-profit organization that is working to improve methods for developing new medical products through precompetitive sharing of data and knowledge. C-Path has established a number of collaborations, several of which are receiving support through the CPI, through either congressionally directed funding or other mechanisms. All members of C-Path's formal consortia sign a legal agreement that addresses confidentiality, anti-trust, intellectual property ownership, and related issues. The three collaborations receiving support from CPI are described briefly here.

   • Patient-Reported Outcomes (PRO) Consortium

   The PRO is a collaboration of 24 pharmaceutical companies, formed to develop, evaluate, and qualify instruments to evaluate patient reported outcomes during clinical trials. The instruments will evaluate patient reports related to safety and effectiveness in a number of disease/condition areas: asthma, depression, irritable bowel syndrome, diabetes, mild cognitive impairment, and breast and lung cancer. The goal is to qualify a single PRO instrument for a disease, which will reduce the effort of regulatory scientists to validate instruments used to generate data submitted as part of marketing applications.

   • Coalition Against Major Diseases (CAMD)

   Comprising 13 pharmaceutical companies and 6 patient advocacy organizations, CAMD is working to define standards for common clinical data elements for use in pooling data from the control arms of pharmaceutical clinical trials to develop quantitative disease progression models for Alzheimer's and Parkinson's diseases. CAMD is also working to

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[7] 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.

[8] 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 Web site (www.trialstransformation.org).

identify imaging, biochemical, genetic, and molecular biomarkers that have the greatest potential to identify patient populations that are pre-symptomatic and likely to benefit from new therapies. The collaboration is leveraging efforts already underway in these areas, hoping to achieve broad consensus on methods to advance product development.

3. **Tropical Diseases, Especially TB**. As noted in Senate Report 111-039, there is an urgent need for new treatments for tropical diseases, and in particular for TB. Several of the projects described in this report target those conditions. Anchoring this work are five competitive awards, made through a Request for Application, at the end of September: [9]

   - ***Aeras Global TB Vaccine Foundation*** -- for the discovery of biological and immunological biomarkers for TB vaccines
   - ***The Global Alliance for TB Drug Development*** -- to develop a repository of clinical trial specimens (the Frozen Trial Initiative) and to qualify new preclinical models for the development of TB drug combinations
   - ***The University of Georgia Research Foundation, Inc.*** -- to develop a diagnostic for latent TB
   - ***Colorado State University*** -- to qualify small molecule biomarkers of TB treatment, relapse, and cure
   - ***The University of Utah*** -- to develop and validate point-of-care tests for TB (ultrasensitive SERS detection technology for low concentration antigens)

4. **Bioinformatics Projects**. For the past decade, FDA has been working hard to move from a paper-based to an electronic system for receiving, managing, storing, and sharing data on the products it regulates. 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. To support this huge undertaking, many projects are under way. A key project is the development, approval, and implementation of data standards, the building blocks of many other FDA information technology projects. Structured Product Labeling (SPL) is a data standard for product information FDA has already implemented in multiple areas — medical product labels[10] and establishment registration and listing information is being submitted to FDA in the SPL format. Individual Case Safety Reports (ICSR) is a data standard for adverse event reporting that FDA has already implemented for medical device and animal drug adverse event reporting. The Unique Ingredient Identifier (UNII) is a data standard for substance identification that FDA has already implemented for drug and food products. Additional projects to use data standards to make the management of product information more efficient are in development or being implemented. The OCPP has been supporting the following IT projects:

   - Work with the National Library of Medicine to develop a system to enable FDA staff and the public to identify and track substances used in medical products (e.g., consumers allergic to a substance will be able to identify all products containing that substance)
   - Develop guidance to encourage the use of standards for electronic gathering and management of source documentation in clinical trials

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[9] For more on the RFA, see www.fda.gov/CriticalPath.

[10] More than 8,500 up-to-date, down-loadable drug labels are available free of charge on the Web page at the National Library of Medicine's DailyMed site. See http://dailymed.nlm.nih.gov/dailymed/about.cfm.

- Collaborate with the National Cancer Institute, develop and pilot a repository and management system, called Janus, that will contain clinical study data submitted to FDA for marketing review
- Develop an FDA Scientific Computing Modernization project to develop and implement new data backup strategies, new UNIX computing environments, new operating system environments, and other systems to improve efficiencies in operations and costs. A modernized assets tracking system for scientific workstations and new networking technologies with high-speed connectivity between scientific systems will improve application review and regulatory decision making.

5. **Optimize Sampling of Laboratory Results for Premarket Safety Assessment.** Streamlining the collection of clinical trial data is one of FDA's priorities under the CPI. Engineering an optimized sampling approach for safety data (e.g., in laboratory testing) could lead to more efficient use of resources and better patient compliance. The goal of this project is to develop a conceptual framework for optimal sampling of safety data to make premarket assessment more efficient. The timing and the frequency of laboratory testing in clinical trials will be analyzed to determine the optimal monitoring schedule. The value of each analyte requested in laboratory panels will be evaluated in predicting or preempting an adverse event. An algorithm will be developed to characterize the most sensitive and specific analytes for safety monitoring. Analytes with little independent predictive value will also be identified.
6. **Regulatory Science Initiative on Novel Research and Science-Based Technologies.** As part of an NIH–FDA Regulatory Science research initiative, an NIH–FDA Joint Leadership Council has been established to spearhead collaborative, innovation activities. An RFA was issued in February to work on critical public health issues. Awards have been made to support innovative clinical trial designs with the goal of accelerating drug and device evaluation. The project addresses how to best use adaptive clinical trial designs to improve the evaluation of drugs and medical devices and proposes to pilot a study on the emergency treatment trials network (NETT), supported by the National Institute of Neurological Disorders and Stroke. Four innovative adaptive clinical trials will be designed to evaluate drugs and devices used in the care of patients with acute neurological illness or injury. Key steps and barriers related to the acceptance and implementation of adaptive clinical trials will then be identified and qualitatively characterized. These projects will not only better inform scientists and regulatory reviewers about medical product safety, but also improve the evaluation process and help make new medical products available to the public.

Center for Biologics Evaluation and Research (CBER) FY 2010 Summary

Center for Biologics Evaluation and Research (CBER)							
	Project	Partnerships	Q1	Q2	Q3	Q4	FY Total Funding
1	Develop effective tools for predicting safety and efficacy of novel adjuvants and vaccine delivery systems	Novartis; CSL; Pevion; GenVac; SAIC/NCI-Fredrick; National Institutes of Health	$0	$25,639	$41,019	$28,143	$94,801
2	Develop and standardize serological criteria for evaluation of new vaccines	Center for Disease Control; Institute of Child Health, London	$0	$0	$12,798	$6,296	$19,094
3	Develop standards for testing cell substrates	American Type Culture Collection	$0	$0	$49,738	$33,240	$82,978
4	Assess the safety and efficacy of polysaccharide-based vaccines	National Institutes of Health; University of Georgia, Athens	$0	$0	$105,581	$8,554	$114,135
5	Develop a Toxoid Antigen Research Program	None identified	$0	$0	$2,864	$17,133	$19,997
6	Evaluate xenotropic murine leukemia retrovirus (XMRV) risk in vaccine cell substrates	None identified	$0	$4,227	$14,436	$38,236	$56,899
7	Characterize novel live attenuated mycobacterial vaccines	Albert Einstein College of Medicine	$0	$0	$30,633	$94,671	$125,304
8	Regenerative medicine: assess safety and efficacy of stem cell-derived products	National Institutes of Health	$0	$0	$8,982	$11,018	$20,000
9	Improve animal models and biomarkers predictive of toxicity of blood substitutes	None identified	$0	$6,744	$20,393	$61,428	$88,565
10	Develop a rapid in vitro screening method to detect insertional mutagenesis of integrating vectors	Hannover Medical School, Germany	$0	$0	$0	$63,800	$63,800
11	Improve the safety and efficacy of adenovirus gene therapy vectors	Baylor College of Medicine; Feinstein Institute for Medical Research (North Shore Hospital)	$0	$5,257	$7,686	$31,066	$44,009

Center for Biologics Evaluation and Research (CBER)							
	Project	Partnerships	Q1	Q2	Q3	Q4	FY Total Funding
12	**Develop preclinical models of vascular endothelial dysfunction to evaluate safety of hemoglobin-based products and aged red blood cells**	National Institute of Neurological Disorders and Stroke; University of Torino, Italy; Academic Medical Center, The Netherlands; Aarhus University, Denmark	$0	$2,135	$6,023	$131,365	$139,523
13	**Improve detection of blood-borne pathogens**	American Red Cross	$0	$0	$35,049	$10,410	$45,459
14	**Develop comprehensive HIV variant viral reference panel**	New York University; National Institute for Biological Standards and Control	$0	$0	$91,126	$31,123	$122,249
15	**Develop product quality biomarkers for stored blood cells**	None identified	$0	$0	$15,098	$44,931	$60,029
16	**Develop assays and reference reagents for blood donor surveillance and virus transmission**	Cleveland Clinic; Whitemore Peterson Institute; National Cancer Institute	$0	$5,173	$18,603	$176,056	$199,832
17	**Develop viral reagents for the evaluation of new and existing assays for the detection of Dengue and Chikungunya**	None identified	$0	$921	$23,075	$19,912	$43,908
18	**Evaluation of blood and vascular biocompatibility of engineered nanomaterials**	National Institutes of Health; National Institute of Standards and Technology	$0	$531	$23,743	$41,683	$65,957
19	**Determine the role of platelet products in transfusion-related acute lung injury (TRALI)**	University of Pittsburgh	$0	$0	$22,918	$25,066	$47,984
20	**Improving the clinical efficacy of hepatitis C immune globulin products**	National Institutes of Health	$0	$833	$9,230	$44,936	$54,999
21	**Developing Laboratory Tests to Screen Blood Donors for Babesia Risk**	None identified	$0	$0	$7,738	$84,232	$91,970
22	**Application of the multiplex allergen extract potency assay to German cockroach allergen standardization**	University of Virginia; National University of Singapore	$0	$0	$34,567	$50,391	$84,958
	Total CBER Funding		**$0**	**$51,460**	**$581,300**	**$1,053,690**	**$1,686,450**

Improve Vaccine Safety. CBER researchers are working on better tools to predict the safety and effectiveness of newly developed vaccine adjuvants and techniques for administering vaccines.

1. **Develop Effective Tools for Predicting Safety and Efficacy of Novel Adjuvants and Vaccine Delivery Systems.** Adjuvants are substances that increase the ability of vaccines to stimulate protective immune system responses. CBER scientists have developed laboratory tests that measure the rise in levels of molecules produced that trigger inflammation in response to adjuvants. The results of these laboratory tests are being correlated with responses in rabbits that receive new, experimental adjuvants. The preclinical evaluations of candidate new adjuvants for an immune response in vitro could assist in the selection of safer vaccines for further development, and could supplement (or reduce) the use of small animal models. Recently, multiple partnerships were established with Novartis, CSL, Pevion, GenVac, SAIC/NCI-Frederick, and the Vaccine Research Center-National Institutes of Health to collaborate and evaluate novel adjuvants and vaccine delivery systems in the new assays (also known as methods of analysis) developed by CBER scientists. As a result of this project, a vaccine sponsor has asked CBER scientists to assist in studies of unexplained adverse events they observed with their product.
2. **Develop and Standardize Serological Criteria for Evaluation of New Vaccines.** Pneumococcal disease continues to be a major cause of morbidity and mortality among both the elderly and the very young. CBER researchers are working to support the development of an effective pneumococcal vaccine for the elderly for distribution in 2011.
3. **Develop Standards for Testing Cell Substrates.** Vaccines are often manufactured using cell substrates. The cell substrates used during the production of these products may be contaminated with viral and bacterial agents. To mitigate contamination risk, CBER requires mandatory testing of all cell substrates. The procedure currently recommended for testing is laborious, costly, and time consuming. The use of nucleic acid amplification technology is considered the most promising approach for developing new methods as alternatives to current manufacturing contamination testing methods. The main goal of this project is to develop standards that can be used to evaluate, validate, and calibrate rapid contamination testing methods of cell substrates and cell-derived biological products.
4. **Assess the Safety and Efficacy of Certain Vaccines.**[11] CBER scientists are using nuclear magnetic resonance spectroscopic characterization – an analytical method that allows the detection of structural information of molecules – to determine the identity, structure, stability, and impurity profile of vaccines. The goal is to reduce or eliminate the need for bioassays – tests that determine the strength or biological activity of a substance, such as a drug, by comparing its effects with those of a standard – which are highly variable and require animal testing, by providing reliable, quantitative data for safety and efficacy of polysaccharide-based vaccines.
5. **Develop a Toxoid Antigen Research Program.** CBER scientists will determine whether antigenicity – the capacity to stimulate the production of antibodies or the capacity to react with an antibody – of botulinum toxoids predicts potency in a mouse model. Historically, botulinum antigens have been tested in guinea pigs and more recently in mice. The goal is to reduce in-process animal testing by developing a test that can be used to identify and

[11] A *polysaccharide* is any carbohydrate made up of a chain of monosaccharides. Starch, cellulose, and glycogen ("animal starch") are polysaccharides.

eliminate sub-par vaccine lots prior to performing release potency tests. The test could also be used to augment or replace animal testing during product release and stability testing.

6. **Evaluate Xenotropic Murine Leukemia Retrovirus (XMRV) Risk in Vaccine Cell Substrates.** A novel gamma-retrovirus, XMRV-related virus has recently been found in humans with chronic fatigue syndrome and prostrate cancer. In addition, infectious retrovirus has been isolated from patient plasma. The origin and mode of transmission of this retrovirus in humans remains unclear. Because this retrovirus is potentially involved with disease, it is important to rid this novel human retrovirus from vaccines, especially for novel tumorigenic and tumor-derived vaccine cell substrates, which generally have an unknown donor and cell passage history. Researchers have developed polymerase chain reaction assays for XMRV detection to screen vaccine cell substrates for the presence of XMRV and to evaluate susceptibility of the vaccine cells to virus infection. Results from the assays will enable researchers to evaluate whether it is necessary to implement additional testing or viral clearance steps in vaccine manufacture to ensure the absence of XMRV.

7. **Characterize Novel Live Attenuated Mycobacterial Vaccines.** Despite being an ancient disease, tuberculosis (TB) remains one of the most devastating causes of morbidity and mortality worldwide. For this CPI project, CBER researchers evaluated the safety, immunogenicity, and protective effectiveness of several promising vaccine strains. At least one of the vaccine strains is a viable human vaccine candidate. The results of this project should contribute to the development of an improved vaccine against tuberculosis.

Promote Development of Innovative Therapies. CBER is working on the following projects to promote public health by facilitating the invention and development of safe and effective novel therapies, including cancer therapy, blood substitutes, and regenerative cell therapy.

8. **Regenerative Medicine: Assess Safety and Efficacy of Stem Cell-Derived Products.** Neural stem cells isolated from adult, fetal, and embryonic sources have been proposed for use in the treatment of Parkinson's disease, Alzheimer's disease, and spinal cord injury. However, the development of these cells as therapies depends on the identification of reliable biomarkers[12] that predict whether specific neural stem cell products will provide clinical benefit after they are transplanted into patients. CBER scientists are working to determine if a protein called Notch2 can be used as a biomarker to support the development of new stem-cell based products for tissue regeneration. The experimental results using mouse cells have shown that Notch expression and activity directly correlate with cellular features normally associated with neural stem cells. Expression of Notch can be used as an indicator of the differentiation status of neural stem cells, which is a critical characterization feature needed for cell-based products. CBER scientists are now studying human stem cell derived neural precursor cells to determine if Notch performs a similar function in this potential cell source for regenerative therapies.

9. **Improve Animal Models and Biomarkers Predictive of Toxicity of Blood Substitutes.** CBER researchers are working to develop ways to predict whether newly developed blood-substitute products, called hemoglobin-based oxygen carriers (HBOCs), are toxic. HBOCs are designed to carry oxygen to cells when the level of red blood cells is low due to blood loss and are designed for use when transfusions of donated blood are not possible or impractical. CBER is pursuing this goal by improving animal models used to test HBOCs and by identifying biomarkers that predict toxicity of these products. The ability to predict the safety and effectiveness of HBOCs will significantly assist in developing these products.

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[12] A *biomarker* is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

The findings related to this work were recently published suggesting that it might be possible to design safer HBOCs.

10. **Develop a Rapid In Vitro Screening Method to Detect Insertional Mutagenesis of Integrating Vectors.** The field of gene therapy lacks necessary, rapid screening assays to facilitate development of safe and effective new vector systems. CBER researchers are working with researchers at the Hannover Medical School in Germany to develop an in vitro cell culture-based method and assess the relative sensitivity and specificity of detection of vector-mediated cell immortalization to be used as an initial screen of new vectors for potential tumorigenic risk in vivo. Having a more rapid way to assess vectors may encourage innovation and ultimately lead to identifying a novel vector design with reduced risk of cancer in patients while retaining the therapeutic benefit from delivery of the necessary gene to treat disease.

11. **Improve the Safety and Efficacy of Adenovirus Gene Therapy Vectors.** CBER scientists are investigating how the adenovirus (Ad) vector used to ferry therapeutic genes to their target can cause toxic reactions in the body. As part of this effort the researchers are trying to develop better animal models to evaluate the safety of these vectors. The goal is to help CBER product reviewers interpret preclinical animal safety studies of treatments using these vectors and to compare the risks and benefits for patients in clinical trials. CBER researchers are also working to find ways to decrease the toxicity of Ad vectors as well as to improve understanding of preclinical animal models.

12. **Develop Preclinical Models of Vascular Endothelial Dysfunction to Evaluate Safety of Hemoglobin-Based Products and Aged Red Blood Cells.** Controlled trials on hemoglobin-based oxygen carriers (HBOCs) have provided the most in-depth information on the potential harmful effects of extracellular hemoglobin highlighted by severe adverse events such as myocardial infarction and stroke. A lack of preclinical models, particularly of vascular disease, inflammation, and antioxidant depletion as well as preclinical safety markers for extracellular hemoglobin toxicity, hinders CBER's ability to adequately predict clinical safety with current and future HBOC candidates and stored blood. The goal of this project is to evaluate three independent models of endothelial dysfunction, including atherosclerosis, inflammation and antioxidant depletion with a focus on identifying, quantifying, and validating selected and reproducible preclinical markers of endothelial injury or activation. During 2010, substantial progress has been achieved in the development of the atherosclerosis model, and several key vascular biomarkers were established to facilitate the evaluation of vascular disease conditions (e.g. stroke) and to monitor the safety and efficacy of therapeutics for vascular diseases. Upcoming studies will continue to address key scientific gaps in our understanding of the interplay between disease state and therapeutics by evaluating preclinical safety concerns that may not have been previously detectable or adequately considered.

Continue Efforts to Ensure Blood and Blood Product Safety. A major CBER responsibility is to protect the nation's blood supply from contamination and ensure the safety and efficacy of blood products. CBER researchers are developing tools to detect disease-causing microorganisms in donated blood and blood products.

13. **Improve Detection of Blood-Borne Pathogens.** The goal of this project is to address the current lack of laboratory tests to detect several important infectious parasites in blood donors. CBER scientists are working to develop a test for the parasite that causes Chagas disease, a potentially fatal infection that affects the heart and other organs. This test, which uses small molecules of nucleic acid that bind to the parasite, has a success rate of over 60 percent in finding the parasite in donated plasma. Nucleic acids are the building blocks of

DNA. More recently, CBER scientists discovered specific small molecules of nucleic acid that recognize a conserved protein on the surface of the parasite. This small molecule of nucleic acid could be a key part of a test designed to detect the parasite in blood and facilitate efforts to eliminate it.

14. **Develop Comprehensive HIV Variant Viral Reference Panel.** CBER regulates donor screening assays and HIV diagnostic tests, which are critical for identifying individuals infected with the virus and managing patients on therapy. The usefulness of such tests is threatened by the tendency of this virus to mutate inside patients. Therefore, in collaboration with New York University, CBER researchers are developing reference materials to standardize and evaluate the performance of these new HIV assays and ensure their accuracy. As a result, two HIV strains were added to the FDA panel for blood and plasma donor screening. These new panels were developed because there have been several reports in the published literature suggesting that the newly added strains are either not detected or under quantified by current assays. Having these reagents will help CBER with approval and postmarket surveillance of HIV assays.

15. **Develop Product Quality Biomarkers for Stored Blood Cells.** Currently, there is no single in vitro marker that serves as the gold standard for predicting the quality of stored blood cells – red cells and platelets. Therefore, CBER scientists are working to identify genomic biomarkers that can reliably predict the quality of stored blood cells. These biomarkers would ultimately fulfill an unmet need to quickly determine if stored blood can be safely used for transfusion and would also prepare CBER for future regulatory challenges in the area of blood safety and testing. As part of this work, CBER scientists demonstrated the presence of tiny pieces of RNA, called microRNAs, that block messenger RNA from making proteins in platelets. The scientists also detected changes in a few specific types of miRNAs that are linked to apoptosis — cell suicide. As new miRNAs are discovered, they will be included in the study. CBER researchers are studying whether these miRNAs could be developed into reliable quality biomarkers for stored blood cells.

16. **Develop Assays and Reference Reagents for Blood Donor Surveillance and Virus Transmission.** It is critical to develop sensitive test methods and well-characterized reference reagents to standardize assays from different labs and ensure accuracy of diagnostic findings. The reference panels will be used for lot release testing of kits in the event testing of the blood supply becomes necessary. These tools will also be needed to perform studies of prevalence, distribution, virus infectivity and transmission to clarify and corroborate the findings of xenotropic murine leukemia retrovirus (XMRV) that have been reported so far. Recently, polymerase chain reaction assays were developed to detect XMRV and were evaluated in a collaborative study coordinated by CBER scientists. In addition, CBER scientists have cultured large quantities of XMRV and the heat-inactivated stocks will be made available to collaborating labs to obtain a consensus value for the stocks prior to formulation of panel tests. The availability of these panel tests will help manufacturers in the efforts to develop assays for XMRV.

17. **Develop Viral Reagents for the Evaluation of New and Existing Assays for the Detection of Dengue and Chikungunya.** CBER scientists are preparing reagents to evaluate new and existing tests for two mosquito-borne infections, dengue fever and chikungunya. Dengue is a potentially fatal disease that causes high fever, severe headache, and severe pain in the joints, bone, and behind the eyes. Cases in the United States have been found as outbreaks in localized areas such as Puerto Rico, Texas-Mexico borders, and Florida, as well as among travelers to areas where this disease is common, such as South America and the Caribbean. Chikungunya, which occurs mostly in Africa and Asia, causes symptoms similar to dengue.

CBER researchers are working to establish specifications for tests that identify these viruses in patient samples to fulfill the center's regulatory role over these products. This work is focused on making reference viral reagents, such as purified viruses or viral components and the antibodies that recognize them. Recently, CBER scientists characterized the Dengue stock reagent in collaboration with other laboratories from the government, academia, and industry, and the reagent is currently under investigation for stability. Next, CBER scientists will partner with the World Health Organization for international characterization and to finalize the formulation for global distribution. This reagent will be used for evaluation and standardization of assays to detect Dengue.

18. **Evaluation of Blood and Vascular Biocompatibility of Engineered Nanomaterials.** Nanotechnology has developed very rapidly in recent years, resulting in an ever-increasing production of various derivatives of carbon fullerenes and various types of carbon nanotubes (CNTs). CNTs may be added to various plastics, including those used in blood collection devices. However, the compatibility of these nanomaterials with blood and blood vessels has not yet been demonstrated. CBER researchers have investigated interactions of blood platelets with CNTs and demonstrated the platelet-aggregating activity of different single-walled and multi-walled CNTs. In addition, they found that CNT-induced platelet activation may be prevented by specific compounds, such as calcium entry inhibitors. They also showed that CNT-induced platelet activation is associated with a marked release of platelet membrane microparticles containing proteins called CD62P and CD63. These proteins are linked to the release of various molecules from platelet granules that are involved in clotting and other functions of the platelet. These proteins could serve as biomarkers for the activation of platelets by CNTs. Recently, CBER researches showed that CNTs have pro-thrombotic (blood clotting) activity since they are able to activate blood platelets, which plays a key role in the thrombus formation. They identified the molecular mechanism by which CNTs cause this effect. This is critical in evaluating toxicity of these unique nanomaterials, which are extensively investigated for various biomedical applications.

19. **Determine the Role of Platelet Products in Transfusion-Related Acute Lung Injury (TRALI).** TRALI is the most frequent biologically based, transfusion-associated mortality event reported to FDA, and it has been reported with all transfusion products. TRALI has been found to be associated with administration of platelets treated with pathogen reduction (PR) processes. Pathogen reduction is the addition of a chemical with an affinity for nucleic acids to a transfusion product and activation of the chemical with UV light. The pathogen reduction methodology has been shown to be effective in decreasing bacterial, viral, and protozoal pathogen loads of transfusion products in vitro and is considered a promising method for reducing transfusion-transmitted disease. An animal model for human platelet transfusions is being developed to evaluate platelets caused by cellular processing. This model will enable the study of underlying mechanisms of platelet-associated TRALI in more detail so that current and future platelet products can be evaluated for their potential to mediate TRALI.

20. **Improving the Clinical Efficacy of Hepatitis C Immune Globulin Products.** In the majority of patients who are infected with hepatitis C virus (HCV), the virus cannot be effectively eliminated despite the presence of neutralizing antibodies. As a result, HCV infections can become chronic, even developing into liver cirrhosis and cancer (HCV-induced cirrhosis is the leading cause of liver transplantation in the United States). HCV-specific intravenous immune globulin (HCIGIV) has been studied as a treatment option. But current HCIGIV fails in preventing HCV re-infection after transplantation in clinical trials. Currently, one requirement for generating an effective HCIGIV is a potency assay that predicts clinical effectiveness. The goal of this project is to establish a potency assay that

can measure the level of HCV-neutralizing antibodies in individuals who have received HCIGIV during clinical trials. Ultimately, our studies should facilitate the development of effective HCIGIV.

21. **Developing Laboratory Test to Screen Donors for Babesia-Risk.** Babesiosis is a tick-borne zoonosis caused by infections of humans with intra-erythrocytic protozoa of the genus Babesia. Babesiosis is locally prevalent in diverse regions of the United States. Some of the infected individuals can carry asymptomatic, chronic infections that are difficult to recognize and, transfusion of blood and blood components collected from them may result in transfusion-transmitted babesiosis, leading to potentially fatal clinical illness. The highest numbers of both tick-borne and transfusion-induced Babesia infections occur in the United States. Despite this persistent and increasing public health concern, there is no approved laboratory test for blood donor screening or any FDA guidance or policy to identify and defer Babesia-risk blood donors. This project will fill a critical gap in blood safety by developing novel DNA based and antibody based tests to detect Babesia infections in blood donors.

Ensure Allergen Potency. CBER has a responsibility to ensure the safety, efficacy, and potency of allergenics. Allergenic extracts are injectable products made from natural substances – such as mold and pollens – that elicit allergic reactions in susceptible people. They are used for the diagnosis and treatment of allergic diseases.

22. **Application of the Multiplex Allergen Extract Potency Assay to German Cockroach Allergen Standardization.** Allergenics are complex products that contain many different extracted components of allergen source material. Previous studies performed by CBER researchers found that current tests of the overall potency of products that contain a variety of allergens can fail to detect potentially significant changes in the amounts of individual allergens. Thus, large differences in amounts of specific allergens can go undetected if overall potency assays are used. CBER scientists are developing a multiplex allergen extract potency assay to assess the quantities of each individual component and use the results to provide an improved overall assessment of the potency of the entire mixture. This method has been applied successfully to cat and short ragweed pollen allergen extracts. The scientists will adapt the assay to other extracts: cockroach, dust mites, grass pollens, food, and molds.

Center for Drug Evaluation and Research (CDER) FY 2010 Funding Summary

Center for Drug Evaluation and Research (CDER)							
	Project	**Partnerships**	**Q1**	**Q2**	**Q3**	**Q4**	**FY Total Funding**
1	**SAFEKIDS**	Harvard/Boston Children's Hospital. Columbia University, Mayo Clinic, University of Arkansas	$0	$0	$0	$750,000	$750,000
2	**Electrocardiogram (ECG) Warehouse Streamlining clinical trials for assessing new drugs potential to delay cardiac repolarization**	Mortara Instrument, Milwaukee, WI	$0	$0	$0	$660,000	$660,000
3	**Collaborations on Innovative Projects**	Critical Path Institute, Tucson, AZ	$0	$0	$0	$525,000	$525,000
4	**Analgesic Clinical Trial Innovations, Opportunities, and Networks (ACTION) Initiative**	University of Rochester, University of Pennsylvania, University of Pittsburgh	$0	$0	$0	$999,940	$999,940
5	**Antiviral Information Management System (AIMS) to improve clinical trial design and analysis**	None at this time.	$0	$0	$0	$100,000	$100,000
6	**The Relationship Between Imaging Biomarkers and Clinical Response in Multiple Sclerosis Drug Development**	None at this time.	$0	$0	$0	$83,113	$83,113
7	**National Institute for Pharmaceutical Technology and Education (NIPTE)**	The National Institute for Pharmaceutical Technology and Education, Des Plaines, IL (NIPTE; NIPTE members are universities)	$0	$0	$0	$239,946	$239,946
	Total CDER Funding		**$0**	**$0**	**$0**	**$3,358,000**	**$3,358,000**

CDER Project Summaries

1. **SAFEKIDS.** This initiative will evaluate the safety of key inhaled and intravenous anesthetic drugs in children by comparing effects of regional and general anesthesia on neuro-developmental outcomes in infants and sibling pairs. Research is urgently needed to fully determine the neurological and developmental effects in pediatric patients exposed to these agents.

2. **The ECG (Electrocardiogram) Warehouse. Streamlining Clinical Trials for Assessing New Drugs' Potential to Delay Cardiac Repolarization.** FDA, in partnership with Mortara Instruments, has established an ECG Warehouse, which now contains more than two million digital ECGs. The project will expand the capabilities of the ECG warehouse, develop new statistical evaluation methods and quality control metrics, and determine if there are important differences in baseline and drug-induced QTc prolongation across ethnic groups.

3. **Collaborations on Innovative Projects.** FDA has established a public-private partnership with the C-Path Institute to support activities of various collaborations. CDER is supporting the Predictive Safety Testing Consortium, which is bringing together multiple stakeholders to share and validate markers of kidney, liver, and muscle injury as well as carcinogenicity.

4. **Analgesic Clinical Trial Innovations, Opportunities, and Networks (ACTION) Initiative**. There is an urgent need to develop new effective and safe analgesics or painkillers. Through public-private-partnerships, multiple scientific projects will be conducted. It is anticipated that the ACTION Initiative will be a multi-phased, multi-year effort that will include clinical and nonclinical projects as well as over-arching coordination and program management activities.

5. **Antiviral Information Management System to Improve Clinical Trial Design and Analysis.** This initiative will develop a framework to improve dose selection for hepatitis C Virus drugs by developing a structured database and analysis tools to enable proposed trials to be evaluated for dose and trial design decisions.

6. **Multiple Sclerosis Drug Development – The Relationship Between Imaging Biomarkers and Clinical Response in Multiple Sclerosis.** To accelerate the pipeline for drugs to treat multiple sclerosis, disease progression and disease response, models will be developed using data from the FDA regulatory database. These models will have the potential to improve clinical trial design and analysis and establish the relationship between MRI parameters and clinical endpoints.

7. **The National Institute for Pharmaceutical Technology and Education (NIPTE) -** Manufacturing training contract to assess the needs, then design, develop, implement, and evaluate a 3-tiered program to train FDA CMC reviewers in the Office of New Drugs, the Office of Generic Drugs, and the Office of Biotechnology Products on state-of-the art pharmaceutical manufacturing technologies. To be able to efficiently review pharmaceutical marketing applications and encourage manufacturers to use modern manufacturing techniques (e.g., quality by design techniques), FDA reviewers need to remain up-to-speed on the latest manufacturing technologies.

Center for Devices and Radiological Health (CDRH) FY 2010 Summary

	Center for Devices and Radiological Health (CDRH)						
	Project	**Partnerships**	**Q1**	**Q2**	**Q3**	**Q4**	**FY Total Funding**
1	**Quality of life and significant symptoms after LASIK**	National Eye Institute (NIH) and Department of Defense	$0	$0	$599,051	$395,949	$995,000
2	**Development and validation of a standard test method to assess for impingement of artificial total disc replacement devices (TDRs)**	Exponent, Inc (Philadelphia, PA)	$0	$5,354	$347,504	$0	$352,858
3	**Standardization of computational fluid dynamic (CFD) techniques used to evaluate performance and blood damage safety in medical devices**	University of Pittsburgh, Cleveland Clinic Foundation, Mississippi State University, Rochester Institute of Technology, Penn State University	$0	$2,000	$163,582	$10,265	$175,847
4	**Re-thinking analytical strategies for surveillance of medical devices**	Harvard University Center for Medical Technology Policy	$0	$0	$252,126	$132,860	$384,986
5	**Accelerating the regulatory process for translation of nanotechnology based products into medical devices & diagnostics**	NIH Nanoparticle Characterization Lab	$0	$0	$0	$0	$0
6	**Optimization of preclinical test methods for simulating the degradation of bioabsorbable implants**	Instron, Vaupell Midwest Molding and Tooling, Spectrum Plastics	$0	$7,216	$43,013	$0	$50,229
7	**A new paradigm in medical device design and evaluation: leveraging the simulation-based engineering and medical imaging technology revolutions in Critical Path research**	Dartmouth University, M2S, Cleveland Clinic Foundation, SFA Stent Manufacturers, University of Colorado	$0	$7,380	$46,620	$50,000	$104,000
8	**Optimizing clinical trial design for the development & advancement of pediatric cardiovascular devices: workshop**	American Academy of Pediatrics (AAP), American College of Cardiology (ACC), Society for Cardiovascular Angiography and Interventions (SCAI)	$0	$0	$0	$24,979	$24,979

Center for Devices and Radiological Health (CDRH)							
	Project	Partnerships	Q1	Q2	Q3	Q4	FY Total Funding
9	**The assessment of molecular diagnostic assays as alternative reference methods for premarket evaluation of rapid molecular diagnostic devices for influenza**	None at this time.	$0	$88,000	$45,000	$0	$133,000
10	**Facilitate machine assisted signal detection using semantic text mining**	IBM	$0	$0	$258,800	$0	$258,800
11	**Optimization of defibrillation in children using computational modeling**	Johns Hopkins University, Cardiosolv	$0	$0	$247,805	$0	$247,805
12	**Comparison of image quality and dose using CT and tomosynthesis modalities**	National Navy Medical Center	$0	$54,300	$110,700	$0	$165,000
13	**Determine if computer simulations of semi-autonomous drug administration devices with incorporated pharmacokinetic/pharmacodynamic models can be used to improve premarket study design, enable prediction of the boundaries of personalized dosing, and reduce postmarket adverse events**	National Naval Medical Center	$0	$0	$48,200	$29,700	$77,900
14	**Apply computational intelligence in medical device study: developing a composite index approach to predicting individual patient success outcomes after lumbar disc implantation.**	National Institutes of Health, Social and Scientific Systems	$0	$2,600	$132,400	$0	$135,000
15	**Standardized use of brain fMRI as a biomarker for clinical trials**	National Institutes of Health, Nordic Neuro Lab	$0	$0	$15,275	$11,691	$26,966
16	**Ensure the safety and effectiveness of neurodiagnostic and psychometric devices for vulnerable patient populations: workshop**	None at this time	$0	$0	$0	$83,000	$83,000

Center for Devices and Radiological Health (CDRH)							
	Project	Partnerships	Q1	Q2	Q3	Q4	FY Total Funding
17	**Develop a registry for intraocular lens implants: a method of surveillance for inflammatory syndromes and adverse events**	University of Utah, ASCRS, Outcomes Sciences Inc.	$0	$0	$0	$140,000	$140,000
18	**Risk-benefit and decision analyses of electro-convulsive therapy in major depression, mania and schizophrenia**	Center for Medical Technology Policy	$0	$0	$0	$115,000	$115,000
19	**Enabling whole-slide digital microscopy by developing standard assessment methods for color, dynamic range and 3D viewing of pathology tissue samples**	None at this time	$0	$0	$130,000	$0	$130,000
20	**Investigation of multiplex protein arrays for detecting biomarkers predictive of chemotherapy sensitivity-resistance in breast carcinoma patients**	Northwestern University	$0	$0	$90,000	$70,000	$160,000
21	**Congenital heart disease registry**	American College of Cardiology	$0	$0	$0	$200,000	$200,000
22	**Safety of live case presentation at cardiovascular conferences**	Medstar Research Institute	$0	$0	$0	$75,000	$75,000
23	**VA FDA SAFE (survival analysis of existing) implantable cardioventer defibrillator (ICD) leads collaborative study**	Veterans Administration	$0	$0	$63,000	$0	$63,000
24	**Development of a cardiac electrophysiological device scientific resource**	University of Alabama, Birmingham	$0	$0	$90,003	$9,358	$99,361
25	**Develop analytical software tool to measure variability**	University of Maryland	$0	$0	$0	$55,035	$55,035
	Total CDRH Funding		**$0**	**$166,850**	**$2,683,079**	**$1,402,837**	**$4,252,766**

CDRH Project Summaries

1. **Continue the Quality of Life and Significant Symptoms after LASIK.** Laser-assisted in situ keratomileusis (LASIK) is a surgical procedure that uses an excimer laser to permanently change the shape of the cornea. The goal of the LASIK Quality of Life Collaboration Project is to determine the percentage of patients with significant quality of life problems after LASIK surgery and identify predictors of these problems. The results of the project will help identify factors that can affect quality of life following LASIK and other ophthalmological surgeries and potentially reduce the risk of adverse effects that can impact the surgical outcome.

2. **Develop and Validate a Standard Test Method to Assess for Impingement of Artificial Total Disc Replacement Devices (TDRs).** Impingement of TDRs occurs when the device reaches the limits of functional motion, which can lead to loss of device function. The overall goal of this project is to incorporate impingement characterization testing into premarket evaluation and FDA guidance documents to help better predict which TDR devices will be clinically successful. The first goal of the project, to model spinal impingement by determining design-related complications that lead to impingement, has been completed. The second goal of the project, retrieving worn explants in order to begin comparing the actual device failures to the models, has also been completed.

3. **Standardize Computational Fluid Dynamic (CFD) Techniques Used to Evaluate Performance and Blood Damage Safety in Medical Devices.** CFD methods for describing flow patterns and fluid forces are increasingly being used in the development and premarket and postmarket evaluations of blood-contacting medical devices. The goal of this project is to standardize computational fluid dynamic techniques needed to effectively evaluate performance and assess blood damage in medical devices. A best practices guidance document and a standard are currently under development.

4. **Re-think Analytical Strategies for Surveillance of Medical Devices.** The current paradigm for acquiring and integrating clinical information in real-world settings needs improvement. This project aims to develop and illustrate different methodological approaches to combining and analyzing data from external postmarket databases and integrating them into CDRH postapproval decision making. The goal of this project is to develop the framework using preclinical, clinical, and postmarket information in a continuous manner rather than a 'pass-fail' approach using a cardiovascular device study to demonstrate the tool to then be applied to other devices.

5. **Accelerate the Regulatory Process for Translation of Nanotechnology-Based Products into Medical Devices & Diagnostics.** Current trends in nanotechnology development indicate that FDA needs to be involved in developing processes for issues regarding nano-devices and nano-diagnostics. The Nanotechnology Reviewer Network has been established to fulfill at least three major goals: share reviewer knowledge base, leverage collaboration between industry, academia, and FDA, and develop thought papers and guidance documents for evaluating nanotechnology devices to ensure a consistent approach to the premarket review of products that include such technology. A workshop was held on September 23, 2010. A public docket is currently open to receive comments on how FDA should develop processes regarding nano-devices and diagnostics.

6. **Optimize Preclinical Test Methods for Simulating the Degradation of Bioabsorbable Implants.** Bioabsorbable polymers are currently being used as raw materials for new orthopaedic and cardiovascular medical devices. CDRH is now receiving regulatory submissions using bioabsorbable polymers in load-bearing devices, such as stents, spinal

cages, and tissue engineered products. The primary goal for this project is to quantify the effect of mechanical load on the degradation and strength retention of bioabsorbable implants. To accomplish this goal, test methods that characterize the mechanics and chemical characteristics in bioabsorbable medical device forms exposed to mechanical loads are under development. CDRH is also working with standards organizations on the development of standard test methods.

7. **A New Paradigm in Medical Device Design and Evaluation. Leverage the Simulation-Based Engineering and Medical Imaging Technology Revolutions in Critical Path Research.** Computer simulation methods can help determine the most sensitive and critical design areas to improve the understanding of anatomies and physiologies. The goals of the project are: to promote the use of computational modeling in cardiovascular design and evaluation; address barriers to implementation of computational modeling; and develop reference data, guidance documents, white papers or other tools to integrate computational modeling into regulatory evaluation of cardiovascular devices. Specific activities include: (1) Characterization of Human Aortic Aneurysm Anatomy Project – CHAP; (2) assessment of plaque composition, dynamic biomechanics, and therapeutic outcomes in subjects implanted with endovascular devices - ASPECT-I; (3) coronary artery bifurcation modeling; and (4) interatrial septum modeling.

8. **Optimize Clinical Trial Design for the Development and Advancement of Pediatric Cardiovascular Devices: Workshop.** Identifying clinical trial design elements to encourage the enrollment of pediatric cardiology patients and to maximize data analysis to reasonably predict longer-term outcomes yet maintain high data quality is needed to further the development of pediatric cardiovascular devices. The goal of this project is to reach consensus among the clinical community, industry, and FDA with regard to optimal clinical trial designs for the study of pediatric cardiovascular devices. The workshop was held on September 30, 2010.

9. **Assess Molecular Diagnostic Assays as Alternative Reference Methods for Premarket Evaluation of Rapid Molecular Diagnostic Devices for Influenza.** Rapid diagnosis of influenza is critical for the appropriate patient management in the setting of acute respiratory illness. The goal of this project is to define the relationship between real-time RT-PCR (rRT-PCR) detected viral nucleic acid and infectious virus following influenza infection. The outcome of this project could help improve and expedite FDA's regulatory process for rapid molecular detection devices, facilitating shorter and less burdensome clinical trial designs, and providing more adequate diagnostic devices for public health assessment.

10. **Facilitate Machine-Assisted Signal Detection Using Semantic Text Mining.** Recent advances in unstructured data mining enable use of computers for extracting and analyzing narrative text in electronic documents. The goal of this project is to build a search, retrieval and analysis framework for signal detection and evaluation. The signal detection and analysis framework would provide an efficient means to query across an entire range of documents ranging from premarket submissions to annual reports to adverse event reports.

11. **Optimization of Defibrillation in Children Using Computational Modeling.** The goal of this project is to create a methodology capable of generating unbiased predictions of cardiac defibrillation using patient-specific computational models. The methods and models developed will be used to find the optimum lead placement, shock waveform, and amount of energy needed to be delivered by defibrillators specifically for pediatric patients. The results are intended to be published to provide the scientific basis to advance development and evaluation of defibrillators in pediatric patients and develop new computer modeling

techniques to make the development and use of defibrillators in children more efficient and effective.

12. **Comparison of Image Quality and Dose Using CT and Tomosynthesis Modalities.** Cone beam and 64 slice CT will be compared with a tomosynthesis system for dose and image quality. Dose and image quality will be assessed with three different types of whole body phantoms: male, female, and pediatric. The goal of this project is to investigate whether lower dose tomosynthesis has an equivalent effectiveness of the image quality as a CT scan. Results of this project could lead to reducing the abundance and unnecessary uses of CT with unneeded radiation doses.

13. **Determine if Computer Simulations of Semi-Autonomous Drug Administration Devices with Incorporated Pharmacokinetic/Pharmacodynamic Models Can Be Used to Improve Premarket Study Design, Enable Prediction of the Boundaries of Personalized Dosing, and Reduce Postmarket Adverse Events.** Three closed-loop, semi-autonomous drug delivery products under active development by industry will be evaluated by CDRH and CDER. Semi-autonomous systems are intended to replace selected expertise of healthcare practitioners with devices that automatically respond to monitored variations in patients' physiological signals. The proposed investigation is intended to enable improved understanding of drug delivery devices that use negative feedback control. The goal of this project is to lead to more targeted questions during premarket development and review and to enable more effective signal detection in the post-market period.

14. **Apply Computational Intelligence in Medical Device Study: Developing a Composite Index Approach to Predicting Individual Patient Success Outcomes after Lumbar Disc Implantation.** Computational intelligence models are capable of processing larger amounts of data in an integrated and automated fashion. Artificial lumbar disc replacement is increasingly being used for patients due to an aging U.S. population. The goal is to use a computational intelligence approach to identify factors associated with the patient outcomes and to develop a patient composite index that can predict the patient clinical success outcome after receiving the artificial vertebral disc replacement system.

15. **Standardized Use of Brain Functional MRI (fMRI) as a Biomarker for Clinical Trials.** There is a need to improve clinical endpoints for the safety and effectiveness of medical device and drug therapies. Functional MRI is a popular, non-invasive tool that can assess brain activation and can be used as a biomarker. The project analysis could reveal the optimum fMRI acquisition methods, the reproducibility of fMRI brain signals, sources of variability, and the optimum analysis methods. These results would be used to form a set of standardizations for the use of fMRI as a biomarker for clinical trials.

16. **Ensure the Safety and Effectiveness of Neurodiagnostic and Psychometric Devices for Vulnerable Patient Populations: Workshop.** Neurodiagnostic and psychometric device companies have rapidly expanded the capabilities of their devices, from ones that display collected data to ones with software algorithms that diagnose neurologic and psychiatric disorders. These devices are intended to be used to assess and diagnose vulnerable patients of all ages and for many high-profile disorders such as Alzheimer's, attention-deficit/hyperactivity disorder, depression, seizures or conditions such as depth of drug-induced anesthesia. The goals for the workshop are to discuss the verification and validation of the algorithms to confirm that they are appropriate for the intended patient population, and the information that clinicians and patients/care providers need to understand the output from these devices.

17. **Develop a Registry for Intraocular Lens Implants: A Method of Surveillance for Inflammatory Syndromes and Adverse Events.** Cataract surgery is the most commonly

performed elective procedure in the U.S. population with 5,000 patients per million having the procedure performed annually. Many new intraocular lenses have entered the marketplace and have been associated with adverse events such as increased secondary surgical procedures, secondary cataract formation, elevated intraocular pressure, intraocular infections, and inflammatory syndromes. The goal of this pilot study is to develop a registry that can be used by regulatory agencies as well as clinicians for better understanding factors associated with the development of adverse events and infectious or inflammatory outbreaks in patients who have received intraocular lenses.

18. **Risk-Benefit and Decision Analyses of Electro-Convulsive Therapy (ECT) in Major Depression, Mania and Schizophrenia.** There is a need for a decision analysis model to be developed for ECT use in depressed, bipolar, and schizophrenic patients, with special attention to pediatric and elder populations. The goal of this project is to develop a new model for rational decision making to balance benefits and adverse events of ECT in psychiatric patients so that use of this treatment option will maximize the benefits in accordance with individual patient values.

19. **Enabling Whole-Slide Digital Microscopy by Developing Standard Assessment Methods for Color, Dynamic Range and 3D Viewing of Pathology Tissue Samples.** Recent technological advances in digital microscopy, most importantly, the development of whole slide imaging systems, have accelerated the adoption of digital imaging in pathology. The goal of this project is to develop the necessary assessment methods for color management of digital pathology systems and to explore technologies and methods that will recover, at least partially, the 3D information and wide dynamic range of optical microscopes. Findings can be used to provide recommendations to industry and regulators regarding the limitations and potential gains in accuracy in the assessment of biomarker assessment in surgical pathology.

20. **Investigate Multiplex Protein Assays for Detecting Biomarkers. Individualize Treatments of Chemotherapy Sensitivity-Resistance in Breast Carcinoma Patients.** Current methods for measuring the response of lesional tissue, namely the targeted pathway blockade by these drug agents, have been lacking, with all current approaches suffering from an inability to predict a tumor response to a particular drug treatment. New analytical tools are needed to rapidly monitor tumor response, at a molecular level in a multiplex format, to aid in patient selection. The project goal is to ascertain whether certain biomarkers predict anti-tumor activity and clinical response to therapy and develop a multiplexed antibody array. If successful, the assay would then be validated in xenograft models.

21. **Congenital Heart Disease Registry.** Pediatric congenital heart disease occurs infrequently, is often complex, and requires long-term follow-up. The goal of this project is to develop a registry designed to assess the prevalence, demographics, management, and outcomes of patients with congenital heart disease who are undergoing diagnostic catheterization and catheter-based interventions across the United States. The collection and analysis of these data will facilitate performance measurement, benchmarking, and quality improvement initiatives; and will provide significant contributions to the knowledge base and outcomes associated with congenital heart disease.

22. **Safety of Live Case Presentation at Cardiovascular Conferences.** Live case demonstrations are increasingly performed at cardiovascular scientific meetings. With the increased use of live broadcasts, concerns have been raised about patient safety, the ethics of live broadcasts, and their value as an educational tool. The goal of this study is to evaluate the safety of live case presentations for investigational medical devices. The results of this study will provide significant scientific knowledge on the safety of live case presentations for

investigational medical devices and could provide data for a current guidance document under development.

23. **VA FDA SAFE (Survival Analysis of Existing) Implantable Cardioventer Defibrillator (ICD) Leads Collaborative Study.** This project involves review and analysis of Veterans Affairs (VA) combined clinical and home monitoring data from various VA sources to assemble a new postmarket evaluation tool to estimate failure-free survival and cause-specific failure rates for a variety of contemporary defibrillation leads. The goal is to develop and execute a study plan demonstrating that FDA can partner with the VA to examine existing large repositories of device outcomes data, effectively and retrospectively examine the fate of implanted ICD leads, and provide meaningful long term outcomes data to complement current MDR reporting and Post-Approval Studies.

24. **Develop a Cardiac Electrophysiological Device Scientific Resource.** The specific determinants of cardiac electrophysiology device safety and efficacy remain elusive. The goal of this project is to develop a scientifically-based resource to evaluate the safety, efficacy, and performance of cardiac electrophysiological medical devices to develop a new postmarket evaluation tool, modernize the regulatory process, and develop a tool to aid in the response of urgent public health needs associated with death and serious injury resulting from pacemakers and ICDs.

25. **Develop Analytical Software Tool to Measure Variability.** This tool will be used in clinical trials to help evaluate variability in trials (e.g., in patient response, medical product effectiveness, errors, patient reported outcomes). Currently, this tool is undergoing testing. The test case being used is to measure variability in the benefits to infant health of the use of breast pumps to extend infant intake of breast milk.

Center for Food Safety and Applied Nutrition (CFSAN) FY 2010 Summary

Center for Food Safety and Applied Nutrition (CFSAN)							
	Project	Partnerships	Q1	Q2	Q3	Q4	FY Total Funding
1	**Metagenomic microarray development for gene discovery of enteric pathogens and community analysis of gastrointestinal commensals**	Various State Health Agencies	$53,183	$63,820	$62,436	$13,718	$193,157
2	**Genomic analysis of Cyclospora cayetanensis and Cryptosporidium spp: methods development for organism detection, viability and molecular epidemiological**	University of Georgia	$37,909	$45,491	$45,491	$9,854	$138,745
3	**Assay development for molecular subtyping of Salmonella using the IBIS T5000/6000 biosensor system**	USA/IBIS Biosciences/Abbott Molecular; UK/FERA; University of Maryland	$7,556	$9,067	$9,781	$2,019	$28,423
4	**Electron spin resonance spectroscopy (ESR) studies of factors affecting the antioxidant prooxidant acitivities of dietary supplements**	Dept. of Agriculture	$26,132	$31,358	$37,060	$7,228	$101,778
5	**Whole-genome sequence analysis of salmonella enterica serovars commonly associated with foodborne outbreaks from fresh-cut produce and poultry**	UK/FERA/ Statistics and Informatics Department; University of Maryland	$10,074	$12,089	$13,042	$2,692	$37,897
	Total CFSAN Funding		**$134,854**	**$161,825**	**$167,810**	**$35,511**	**$500,000**

CFSAN Project Summaries

1. **Metagenomic Microarray Development for Gene Discovery of Enteric Pathogens and Community Analysis of Gastrointestinal Commensals**. The human form serves as a habitat for microbes that stably (commensal) or transiently (pathogen) colonizes various regions of the body. These microbes collectively outnumber our own human cells by approximately ten to one. Scientific interest is increasing in characterizing these communities to determine their role in health and disease. The task will involve sophisticated techniques that are accurate and precise enough to determine changes in microbial diversity of enteric pathogens and gut commensals under disease conditions or upon challenge with ingestibles. The project will develop these tools using bacterial DNA sequences that are arrayed for hybridization.

2. **Genomic Analysis of Cyclospora Cayetanensis and Cryptosporidium spp: Methods Development for Organism Detection, Viability and Molecular Epidemiological Applications.** Illness caused by *C. cayetanensis*, *C. hominis*, and *C. parvum* has been associated with contaminated fresh produce and water sources. Pathogen detection using molecular-based approaches has replaced conventional microscopic techniques. PCR is an example of a sensitive molecular-based approach that can quickly detect these pathogenic food-borne and waterborne microorganisms by providing faster diagnostic times plus enhanced sensitivity and specificity. Additional genetic studies of *C. cayetanensis* will increase our understanding of this parasitic pathogen and help develop improved detection methods for use in epidemiological studies and outbreak investigations.

3. **Assay Development for Molecular Subtyping of Salmonella Using the IBIS T5000/6000 Biosensor System**. A mass spectrometry measurement of the PCR amplicons gives a detailed fingerprint of any microbe, providing much more information than many simple yes/no answers provided by current assays. Detection is not limited to previously known organisms. This approach can rapidly identify organisms in a mixture without additional sample preparation steps. The method can be made general or specific and can rapidly identify mutations. The approach can handle many different types of samples and matrices, making it very amenable to food matrices. The approach also enables high throughput, allowing for the analysis of 1,200 samples per 24-hour period.

4. **Electron Spin Resonance Spectroscopy Studies of Factors Affecting the Antioxidant-Prooxidant Activities of Dietary Supplements**. Increasingly, health claims are being made for nutritional antioxidants and dietary supplements. However, the complexity of how antioxidants function in a biological milieu is usually not fully appreciated. This project's goal is to systematically examine the activity of selected dietary supplements under different physiologically relevant conditions, such as variations in the partial pressure of oxygen in tissues, changing concentrations of metal ions, and interactions with other antioxidants. The results will be useful in defining limitations on antioxidant claims for dietary supplements and for framing questions that can be addressed in additional animal or clinical studies.

5. **Whole-Genome Sequence Analysis of Salmonella Enterica Serovars Commonly Associated with Foodborne Outbreaks from Fresh-cut Produce and Poultry**. The ecological complexities of this recurrent contamination of produce by *Salmonella* require the development of more effective and more sensitive DNA sequence-based subtyping methodologies. These methods are important for more rapid and effective responses to *Salmonella*-induced foodborne outbreaks as they should provide vital information on an outbreak's origins, including the produce commodity, the geographic location, and the genetic/epidemiological lineage of the *Salmonella* involved. This project is intended to give

FDA detailed data on the complete genomic structure of a significant number of *Salmonella* pathogens associated with produce-borne outbreaks.

Center for Veterinary Medicine (CVM) FY 2010 Summary

Center for Veterinary Medicine (CVM)							
	Project	Partnerships	Q1	Q2	Q3	Q4	FY Total Funding
1	**Interrogating salmonella diversity using a novel 35 genome salmonella species microarray**	None identified	$0	$464	$501	$0	$965
2	**Evaluation of the potential trans-placental transfer of genetically engineered material from fetus to dam during pregnancy in ruminants**	None identified	$9,089	$710	$3,058	$1,154	$14,011
3	**Evolution of multidrug resistant plasmids in salmonella at the DNA sequence level**	None identified	$0	$1,500	$0	$1,689	$3,189
4	**Application of DNA microarray technology to characterize the inflammatory and immunological responses in swine**	None identified	$2,540	$8,527	$18,863	$18,884	$48,814
5	**Development of novel molecular typing strategies for determining source attribution of salmonella infections**	None identified	$5,693	$0	$244,051	$63,179	$312,923
6	**Developing alternative ivermectin-sensitive model systems & pharmacokinetics of fexofenadine and loperamide in normal and MDR1 mutant collies**	None identified	$296	$101,989	$0	$17,813	$120,098
	Total CVM Funding		**$17,618**	**$113,190**	**$266,473**	**$102,719**	**$500,000**

CVM Project Summaries

1. **Interrogating Salmonella Diversity Using a Novel 35-Genome Salmonella Microarray.** Developing effective ways to characterize and mitigate pathogen contamination of foods requires continued research on the ecology and epidemiology of major food-borne pathogens and improved surveillance of retail food products, including imported products, for microbial hazards. The use of high-density microarrays will enable FDA to obtain a rapid and comprehensive genetic profile of individual *Salmonella* genomes from different sources. This information, in combination with other strain information, will make it possible to define new biomarkers for virulence, antimicrobial resistance, and survival, as well as help us understand the overall genomic diversity of the organism. This study will directly provide a large amount of genomic data that will aid FDA in developing better evaluation tools such as application of microarray technologies to drug development, and in developing better tools to address urgent public health needs such as contamination of food products.

2. **Evaluation of the Potential Trans-Placental Transfer of Genetically Engineered Material from Fetus to Dam during Pregnancy in Ruminants.** The question of the transfer of genetic material from the fetus to the dam could become a food safety concern if authorization is sought to allow ruminants that have served as surrogate dams for genetically engineered (GE) animals to enter the human food supply. The urgency for investigations into the potential transfer of genetic material from the fetus to the dam during pregnancy in goats specifically stems from the recent FDA approval of the first new animal drug application related to a GE animal, in this case a GE goat that produces human antithrombin III in milk, the large number of surrogates used in the production of GE animals that could potentially be sent to slaughter, and additional GE goats awaiting approval.

3. **Evolution of Multidrug Resistant Plasmids in Salmonella at the DNA Sequence Level.** The overall goal of this project is to understand the evolution of plasmid-mediated multidrug resistance in *Salmonella*. Our hypothesis is that drug resistance observed in modern pathogenic *Salmonella* is largely a reflection of plasmid gene accumulation over time following the introduction of novel selective pressures in the form of antimicrobials. The research program will provide insights into the mechanisms of gene acquisition and dissemination that have led to the evolution of the modern resistance phenotypes. The data from this project will be of scientific value in several ways. The problem of resistance in food-borne pathogens is most acute in the salmonellae. The frequency of resistance and the numbers of antimicrobials to which they are resistant is increasing. There is an urgent need to limit or reduce the prevalence of resistant isolates to prevent the incipient development of untreatable strains. This study will provide the first complete catalogue of mobile resistance determinants from various strains of *Salmonella* and shed light on the molecular events leading to the evolution of modern multidrug-resistant isolates.

4. **Application of DNA Microarray Technology to Characterize the Inflammatory and Immunological Responses in Swine.** Nonsteroidal anti-inflammatory drugs (NSAIDs) for use in swine are approved only for control of fever, even though they are also known to control inflammation. This is due to a lack of reliable, validated animal models and biomarkers that can be used to demonstrate the anti-inflammatory nature of NSAIDs. This project will develop the systemic and local inflammatory models in swine needed to support a new animal drug approval along with the appropriate biomarkers that can be used to demonstrate the anti-inflammatory effects of non-steroidal anti-inflammatory drugs.

5. **Development of Novel Molecular Typing Strategies for Determining Source Attribution of Salmonella Enterica Infections.** *Salmonella enterica* is the leading cause of foodborne illness in the United States. Of the more than 2,500 serovars of *Salmonella enterica*, a number of serovars colonize a particular animal host preferentially while others are able to colonize a variety of animal hosts. Identifying bacterial biomarkers in human clinical isolates that are associated with host source would greatly improve the speed and accuracy of tracking outbreaks of *Salmonella*. In particular, S. Typhimurium and Enteritidis are the leading serotypes causing human infection. In addition, the prevalence of multidrug resistant *S. enterica* serotypes from food products has increased in recent years, reducing the therapeutic strategies available for human use. The research will investigate, at the nucleotide level, host range mechanisms of *Salmonella enterica* serotype Typhimurium, the top serotype in human infections.

6. **Developing Alternative Ivermectin-Sensitive Model Systems and Pharmacokinetics of Fexofenadine and Loperamide in Normal and MDR1 Mutant Collies.** The ABCB1 gene encodes for P-glycoprotein (P-gp), which is a membrane protein that affects the absorption, distribution, and elimination of certain drugs. A mutation in this gene occurs in several dog breeds, primarily in herding dogs. Dogs that have mutations in both copies of the gene are at a high risk of developing neurological problems with administration of certain drugs, including avermectins (anti-parasitic drugs). Thus, all new avermectins must be subjected to an additional safety study using ivermectin-sensitive collies. Due to a diminishing number of available ivermectin-sensitive Collie colonies, it is becoming difficult for drug sponsors to get the dogs needed to test the safety of new avermectins. Given the likelihood that studies in this strain of Collie may soon be infeasible, an alternative method is needed to address this safety concern. Therefore, an alternative screening procedure to identify potential P-gp substrates and address safety concerns is needed. Understanding the potential consequences of this defect on the pharmacokinetics of a new drug and the potential for toxicity will improve FDA's ability to predict potential safety and effectiveness of new drugs generally.

National Center for Toxicological Research (NCTR) FY 2010 Summary

National Center for Toxicological Research (NCTR)							
	Project	Partnerships	Q1	Q2	Q3	Q4	FY Total Funding
1	ArrayTrack	None identified	$73,030	$194,413	$58,924	$256,721	$583,088
2	Liver toxicity knowledge base	None identified	$110,949	$142,598	$216,806	$343,373	$813,726
	Total NCTR Funding		**$183,979**	**$337,011**	**$275,730**	**$600,094**	**$1,396,814**

NCTR Project Summaries

1. **ArrayTrack™**. To facilitate the evaluation of complex pharmacogenomic data that are being submitted to FDA as part of the application review process, FDA has developed and is refining FDA's genomic tool, ArrayTrack™. This tool is an integrated informatics infrastructure that is enabling FDA reviewers to evaluate pharmacogenomic, metabolomic, and other -omics data to support regulatory decision making. In collaboration with CFSAN, new modules for facilitating foodborne pathogen identification have been developed. Additional modules to support genetic research for personalized medicine and nutrition have also been developed through this project. These modules enable mapping genetic data related to individual responses to drug treatment to phenotypic information.
2. **Liver Toxicity Knowledge Base**. This knowledge base is being developed to support research into relationships among diseases, pathways, genes and proteins, and drugs. The goal is to enhance our understanding of liver toxicity — more than 25 percent of drugs on the market that ultimately fail and 40 percent that fail during clinical trials fail because of liver toxicity. This project uses a combination of data from the literature on selected drugs along with genomic data from microarray studies to develop a systematic approach to define the severity of risk of a drug for liver injury. These approaches will support the application review process and well as drug labeling activities.