Key FDA Critical Path Activities Under Way in 2007

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Table of Contents

Introduction

In March 2004, FDA described the *critical path to medical product development* and a nationwide effort to move medical product development and patient care into the 21st century in its report "*Challenge and Opportunity on the Critical Path to New Medical Products."*

Two years later, the Agency published a follow-up report, titled "*Critical Path Opportunities Report and List*." The Opportunities Report and List presented 76 specific scientific opportunities that, if undertaken, would provide a starting place for collaborative work on modernizing the critical path sciences. The opportunities were organized into six priority topics and were identified through extensive outreach with patient groups, health-related organizations, the pharmaceutical industry, academia, and other federal agencies. FDA said that the list should not be considered a check list and that over time new activities could easily be added or subtracted. FDA also said that it would announce the specific activities it was undertaking in support of the Critical Path Initiative. In December 2006, FDA published a list of more than 40 collaborations and research activities launched that year.

This update describes key Critical Path activities launched during 2007; in a few cases projects launched during 2006 have expanded in new ways during 2007.[1] This list especially reflects how the Critical Path Initiative has expanded to include all FDA product Centers.

The 2007 activities list continues to be organized according to six priority topics. In a few cases, activities that do not relate directly to one of the six categories are listed at the end of the list in a section called *Other*. The six priority topics are[2]:

- Better Evaluation Tools
- Streamlining Clinical Trials
- Harnessing Bioinformatics
- Moving Manufacturing into the 21st Century
- Developing Approaches to Address Urgent Public Health Needs
- Specific At-Risk Populations — Pediatrics

[1] At the time it was compiled, the list was considered complete. Projects may be under way that qualify as Critical Path activities, but that have not yet been identified as such. All reports are available on the FDA's Critical Path Web page at http://www.fda.gov/oc/initiatives/criticalpath/.

[2] Firm timelines cannot be predicted for projects currently under way. Timing of deliverables depends on our available staff and fiscal resources (we can engage in these projects only to the extent that the work will not draw resources from application review and related regulatory activities). For collaborations, timing will also be affected by the availability of our partners' resources.

TOPIC 1: BETTER EVALUATION TOOLS

Develop Biomarkers to Help Reduce Risk of Disease in Food Producing Animals
Opportunity #1

FDA's Center for Veterinary Medicine (CVM) is conducting a study to identify biomarkers of inflammation in cattle that are related to lipopolysaccharide (LPS) exposure. The importance of the identification of biomarkers indicative of food animal disease stems from (1) the emergence of proteomic methods in research designed to evaluate drug efficacy and (2) a subsequent need for pharmaceutical companies to establish valid proteomic criteria in preapproval drug trials. To date, methods have been developed for the rapid profiling of milk proteins, and protein profiles for both normal and mastitic milk have been generated. Several candidate proteins that are either induced or up-regulated in response to *E. coli* have been identified in bovine milk. Currently, the response of these candidate biomarkers to the administration of non-steroidal anti-inflammatory drugs is being evaluated.

Examine Genetic Basis of Adverse Events
Topic 1: Better Evaluation Tools, Safety Biomarkers

In 2007, the Serious Adverse Events Consortium (SAEC), a nonprofit partnership of several leading pharmaceutical companies, FDA, and academic institutions launched two initial research programs designed to identify genetic markers that may help predict which individuals are at risk for serious drug-related adverse events (SAEs) The two studies will address drug-related liver toxicity and a rare, but serious, drug-related skin condition called Stevens-Johnson Syndrome (SJS). The results from SAEC studies will be made available to the research community. The goal is to provide biomedical researchers and pharmaceutical companies with data on genetic markers that may help address the safety of new drugs in development. FDA plays a scientific advisory role to the SAEC.

Broaden Our Understanding of Drug-Induced Liver Injury
Topic 1: Better Evaluation Tools, Safety Biomarkers

FDA is working with industry, academia, and others to broaden our understanding of the biochemical and genetic basis of drug-induced liver injury (DILI). In 2006, FDA co-sponsored a scientific workshop with Entelos, Inc. to determine the feasibility of an in-silico model for DILI to characterize potential hepatotoxicity. The long-term goal is to collaborate with experts to develop a model, or models, that can help researchers identify when early clinical intervention is appropriate. In August 2007, the FDA entered a two-year Cooperative Research and Development Agreement (CRADA) with Entelos to develop a computer model of DILI. The goal is to use this platform to guide the development of clinical biomarkers and preclinical assays to identify patient types and drug combinations that increase the risk of liver injury.

In October 2007, FDA published a draft guidance for industry on *Drug-Induced Liver Injury: Premarketing Clinical Evaluation* on (the comment period closed on Dec.24, 2007). In conjunction with PhRMA and the American Association for the Study of Liver Diseases (AASLD), FDA held a meeting in March 2008 on detecting and investigating DILI during clinical trials.

Improved Mutation Assays
Opportunity #2

Genetic toxicology assays are used as a part of the safety evaluation for new pharmaceuticals. There is a need to develop new approaches that can be used not only in the rodent assays but also directly in humans that are participants in clinical trials or even eventually as a means to improve postmarket evaluations. In 2007, FDA researchers continued validating the micronucleus assay (a means to detect severe chromosome damage) and have initiated work using the PIG-A gene to detect induced gene mutations. Both of these approaches lend themselves to high throughput detection and, once adequately characterized and validated, should be applicable to preclinical, clinical, and postmarket safety evaluations of pharmaceuticals.

Participate in Microarray Standards Developing Consortia
Opportunity #2

FDA is working with several consortia to develop voluntary consensus standards that would allow application of microarray technologies to drug development and regulatory decision-making.

FDA played a key role in creating the ***MicroArray Quality Control (MAQC) Project Consortium***, which is developing proficiency and analysis standards for laboratory hybridization methods. These standards will enable laboratories to assess their proficiency at microarray experimentation. Suppliers of equipment and RNA samples are among the other MAQC participants. The first phase of the project (MAQC-I) resulted in six scientific papers published in ***Nature Biotechnology***. The papers detailed the perforrmance of the major microarray platforms and a proficiency standard RNA.

During 2007, the efforts of the MAQC expanded to include additional analyses of Genome-Wide Association Study (GWAS) data to help understand the source of variability in the identification of single nucleotide polymorphism (SNP) biomarkers.

FDA also is a partner in the ***External RNA Controls Consortium(ERCC),*** an effort to develop standards for several steps in microarray experimentation, including oligonucleotide sequences (so-called *spikes*), to enable data to be compared across experiments. ERCC is testing the standards developed through this collaboration.

Develop Efficacy Surrogates for Cardiac Drug-Eluting Stent Trials
Opportunity #6

The Cardiovascular Safety and Research Consortium (launched September 2006; http://www.fda.gov/bbs/topics/NEWS/2006/NEW01467.html and www.cardiac-safety.org) originally focused on the development of efficacy surrogates. Attention in 2007 turned to safety issues. FDA, the Duke Clinical Research Institute, and other partners are working closely toward the development of a placebo-controlled, multicenter clinical study of optimal dual antiplatelet regimen for use with drug eluting stents. These efforts are aimed at addressing issues such as myocardial infarction, death, late stent thrombosis, and bleeding events.

Identifying the Relationship Between Efficacy And Safety vs. Immunogenicity of Vaccines
Opportunity #8

FDA has a large database of immunogenicity and efficacy data from vaccine clinical trials. However, the data is submitted in multiple different data formats so that meta-analysis is currently impossible. In 2007, FDA statisticians began work to convert the data into a standardized format so a meta-analysis can be performed to identify the inter-relationships among immunogenicity, safety, and efficacy.

Predicting Safe Cell Substrates for Vaccine Production
Opportunity #54

In a conference in November 2005 funded by the National Institute of Allergy and Infectious Diseases (NIAID), issues and next steps were discussed related to developing streamlined and improved methods for evaluating cells used to manufacture biological products, including vaccines, for (1) the presence of infectious contaminants and (2) the risks of causing tumors. The goal of these efforts was to facilitate the evaluation of the safety and quality of cell cultures proposed for use in influenza vaccine production and new vaccines developed to counter terrorism threats. An FDA NIAID collaboration demonstrated methods for carrying out such evaluations. In 2007, vaccine manufacturers involved in the collaboration began to use these methods to evaluate MDCK (Mason-Darby Canine Kidney) cells for their use in producing the next generation of cell culture derived influenza vaccines. They are characterizing the tumorigenic phenotype of MDCK cells in adult, newborn nude, and transgenic mice and assessing the metabolic pathways involved in establishing these phenotypes. In the meantime, risk models are being developed to better assess the tumorigenic and oncogenic potential of cell substrates for vaccine production. Work on this effort is continuing into 2008.

Safety Biomarkers (C-Path Institute)
Opportunity #20

An activity launched during 2007 (CADRe, the Common Adverse Drug Reaction project) is working to identify genetic markers of important adverse drug events. The workgroup is in the process of identifying a list of potential products and adverse events that they cause, for which a genetic marker would be valuable. Next steps will involve selecting the most useful candidates and listing possible collaborators to perform these studies.

Development of New Predictive Liver Toxicity Biomarkers
Opportunity #20

Teaming with CRADA[3] partner (BG Medicine, Inc), NCTR initiated in 2007 a study using new genomics technologies to discover new predictive biomarkers of liver injury. Such early preclinical biomarkers are needed because currently used biomarkers are not adequate to accurately predict liver injury in humans. Successful development of these biomarkers will result in improved safety assessments of potential new drugs.

Better Safety Biomarkers of Acute Kidney Injury to Improve Public Health and Product Approval
Opportunity #20

FDA and Novartis have been collaborating, under a CRADA, to identify nephrotoxicity biomarkers that predict the effects of drug compounds on kidney function. The goal of this collaboration is the generation of an efficient process map for the validation of genomic biomarkers of preclinical drug safety. The FDA-Novartis CRADA had two primary objectives: (1) To define a process for qualifying preclinical safety biomarkers for regulatory decision making and (2) to test this pilot process by submitting kidney-related safety biomarkers identified and characterized through preclinical studies to the FDA for qualification.

Relevant safety biomarker data generated by Novartis as part of the CRADA have been shared with the C-Path Institute's Predictive Safety Testing Consortium. In 2007, a set of biomarkers

[3] Cooperative Research and Development Agreement.

of nephrotoxicity were submitted to FDA for qualification through a pilot process that is being evaluated at the Agency to understand evidentiary standards and metrics associated with the qualification of novel biomarkers.

Predict Drug Effects on Kidney Function
Opportunity #20

FDA and Novartis have been collaborating, under a CRADA, to identify nephrotoxicity biomarkers that predict the effects of drug compounds on kidney function. The goal of this collaboration is the generation of an efficient process map for the validation of genomic biomarkers of preclinical drug safety. The FDA-Novartis CRADA had two primary objectives: (1) To define a process for qualifying preclinical safety biomarkers for regulatory decision making and (2) to test this pilot process by submitting kidney-related safety biomarkers identified and characterized through preclinical studies to the FDA for qualification.

Efforts conducted under the CRADA have resulted in the publication of the first pilot framework for a preclinical regulatory biomarker qualification process. The development of this process will have a broad impact on the understanding of the qualification of safety biomarkers far beyond this partnership.

In addition, the preclinical data identified thus far have demonstrated evidence for the superiority of new renal biomarkers over the current standards used to assess renal injury in drug testing, namely serum creatinine and blood urea nitrogen (BUN). Further efforts will focus on the extended clinical qualification of biomarkers that could allow clinicians to detect kidney injury in patients earlier than current clinical practice allows.

Relevant safety biomarker data generated by Novartis as part of the CRADA have been shared with the C-Path Institute's Predictive Safety Testing Consortium (PSTC, a larger public-private partnership between industry, academia, and regulatory health authorities intended to serve as a neutral body for coordinating activities related to biomarker qualification in drug development).

Develop Biomarkers to Aid in the Development of Therapies for Polycystic Kidney Disease (PKD)
Opportunity # 15

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common, life-threatening genetic diseases, affecting 600,000 Americans and 12.5 million people worldwide. There is no treatment or cure for PKD. The standard measure of kidney function, glomerular filtration rate (GFR) is accepted as an outcome measure in clinical trials. However, when the measured GFR begins to fall, it is too late for therapeutic interventions to slow or stop the disease. Clinical trials using GFR as a measure of renal function must be carried out over a period of 10 to 20 years to show an effect of a potential therapeutic agent on PKD disease progression.

In May 2007, the FDA co-sponsored a scientific workshop with the PKD Foundation to discuss possible therapeutic targets and novel endpoints for trials intended for drugs to treat polycystic kidney disease. The goal of these and subsequent efforts in 2008 is to help identify potential markers of therapeutics used to slow or stop disease progression.

Validation of Magnetic Resonance Imaging for Assessment and Follow-up of Thermally Ablated Breast Cancers
Opportunity# 26

A consensus regarding standardization for MRI imaging and pathological evaluation of breast cancers is needed for clinical trials evaluating the safety and effectiveness of thermal ablation treatment of small breast cancers in lieu of resection. Such standardization could serve to facilitate data sharing among competing thermal ablation device manufacturers to validate MRI imaging as a biomarker for breast cancer therapies and accelerate development of thermal ablation devices for treatment of breast cancer.

The availability of a validated imaging tool that correlates pathological results with imaging findings would push our understanding of thermally treated cancer further and potentially allow longitudinal studies of breast cancer ablation in lieu of operative resection.

FDA has begun work toward building consensus among industry and academia on how breast cancer thermal ablation trials can be constructed among competing thermal ablation device manufacturers interested in establishing MRI as a biomarker for incomplete tumor ablation and local recurrence of thermally ablated breast cancers

Develop New Preclinical Methods for Predicting Safety and Effectiveness of Gene Therapy for Cancer (Adenovirus Vectors)
Opportunity #30

Adenovirus vectors are being developed as cancer therapies and delivering these gene therapy vectors intravenously would be an ideal way to target widely disseminated metastatic cancer. However, adenovirus vectors are cleared from the circulation within a matter of minutes—so rapidly that they have trouble reaching disseminated tumors. In 2007. FDA scientists began identifying the mechanisms for rapid clearance of adenovirus vectors and developing novel techniques to improve their circulation time and efficiency.

New Tool for Mitochondrial Toxicity
Opportunity #30

Several side effects of anti-HIV drugs including AZT have been associated with altered mitochondrial function. To better understand the molecular mechanism(s) underlying AZT-induced mitochondrial toxicity, a novel genomic approach of MitoChip, an array-based sequencing platform for rapid and high-throughput analysis of mitochondrial DNA, was used in different mouse models. Drug-induced toxic effects on mitochondria were investigated in the liver and skeletal muscle of infant mice exposed before or immediately after birth to AZT. Knowledge gained by using such genomic approach can potentially improve treatment strategies for HIV-infected patients, particularly, infants.

Development of Improved Biomarkers and Animal Models to Predict and Monitor Safety and Efficacy of Blood Substitutes
Opportunity #33

In a program launched in 2007, FDA scientists are establishing improved biomarkers and animal models to enable us to predict and monitor the safety and efficacy of hemoglobin-based oxygen carriers (HBOCs) also known as “blood substitutes.” The proposed project aims at establishing the extent of oxidation of several HBOCs in rats (ascorbic acid “vitamin C” producing) and guinea pigs (none-ascorbic acid producing) animal models and the identification of biomarkers of tissue injury in the heart, kidney and brain. It is anticipated that

we will be able to develop a model approach to more effectively predict the toxicity of HBOCs early in the development process based on the tendency of HBOCs for oxidation and ability to deliver oxygen.

Development of Improved Methods to Measure Potency of Allergen Extracts
Opportunity #33

Allergen extracts are biologics used to treat allergies and asthma, but for most allergen extracts there is no accepted way to measure the potency (strength) of the product. Methods exist to do so, but their relevance to the human response to these products has been questioned. FDA scientists are developing a new, rational, clinically valid and transferable technique to measure the potency of allergen extracts made from German cockroach, which has been implicated as an important cause of asthma, especially in the inner city in the U.S. In addition, improved methods have been developed to determine cat hair, cat pelt, and short ragweed allergen extract potency.

Develop Biomarkers to Help Reduce Risk of Chronic Diseases

Several activities are under way:

- During the period 2005-07 CFSAN has co-sponsored two workshops: (1)the state of the science regarding biomarkers and cancer risk reduction and (2) assessing cardiovascular disease risk and progression with NIH and the Montreal Heart Institute, respectively. The workshops are part of a long-term effort to develop biomarkers that are indicators of disease risk reduction that can be modified by food or a component of food. To support this effort, FDA has begun to assemble a working group consisting of representatives from FDA, NIH, and USDA to identify projects for funding. In addition, CFSAN is exploring related opportunities for collaboration with the National Center for Food Science and Technology (NCFST) in its Health Promoting Foods initiative and will co-sponsor a workshop with NCFST in FY08.

- As a follow-up to the workshops described above, FDA is exploring development of a framework for validating modifiable risk factors (biomarkers) for chronic diseases, such as cancer, heart disease, diabetes, and others that can be the subject of a health claim. The framework will consist of defining the level and type of evidence that is required to support a biomarker that modifies the risk of disease. The first step toward defining a framework will consist of working through the National Academy of Sciences, Institute of Medicine, to convene a panel of experts to outline the steps necessary for qualifying a biomarker for evidence-based decision making, assuming funding becomes available. The task for the panel will be to hold workshops as needed and then to issue a report that FDA can use in its review of scientific evidence offered to substantiate health claims that can be used on food products, including dietary supplements. Funds from the Critical Path initiative have enabled CFSAN to develop a task order with IOM for this initiative.

Develop Tools to Enhance Data Review and Analysis
Topic 1: Better Evaluation Tools

The widely used JMP/Genomics software has been integrated with the FDA genomic tool, ArrayTrack, under a three-year CRADA between NCTR and SAS. ArrayTrak, created by NCTR, is a free bioinformatics resource for DNA microarray and system biology that allows for the management, analysis, and interpretation of -omics data within a single package. The new integrated module allows reviewers and scientists to toggle between both software platforms

to access the analysis functions available from both JMP/Genomics and ArrayTrack for pharmacogenomics data review and analysis.

Training of FDA reviewers through Webinars and/or on-site training for use of ArrayTrack in FDA research and review continues. Several new functions have been developed in ArrayTrack to support the VGDS (Voluntary Genomics Data Submission) program. For example, the CommonPathway tool was developed for integrated analysis of multiple -omics data. The function is important for the VGDS review when multiple -omics data sets have been received from the sponsor. The SAM (Significance Analysis of Microarray) Data method was implemented which enhances our capability to identify genes that are differentially expressed between different treated groups at different doses and time points. The function will result in more accurate gene lists to be carried forward for biological interpretation in the VGDS review process.

TOPIC 2: STREAMLINING CLINICAL TRIALS

(Several of the topics in this section are also relevant to Topic 3: Harnessing Bioinformatics)

Develop Guidances on Advanced Clinical Trial Design

Opportunity #34

A large effort has been under way at FDA during the past several years to encourage the development and use of new trial designs, including enrichment designs. As part of this effort, a series of guidances currently are being drafted that will provide guidance on innovative trial designs. Planned guidances under way include the following:

- Adaptive Trial Designs—publication of a draft is anticipated in 2008. This guidance would explain FDA's perspective on the use of adaptive trial designs during drug development. Topics to be addressed include the definition of adaptive trial designs, recommended designs, and how the statistical issues should be addressed in analyzing trials.
- Non-inferiority Trials—publication of a draft is anticipated in 2008. This guidance would describe FDA's perspective on the design of non-inferiority (NI) trials. Topics expected to be addressed include how to select the active control, how to document the effect size of the active control versus placebo, and how to establish the non-inferiority margin of interest.
- Multiple Endpoints in Clinical Trials—publication of a draft is anticipated in 2009. This guidance would describe FDA's perspective on the appropriate procedures and analyses for trials with multiple endpoints (e.g., a trial with multiple co-primary endpoints).
- Enriched Trial Designs—publication of a draft is anticipated in FY 2010. This guidance would focus on approaches to enrich the clinical trial population to better define the efficacy or safety of the drug under development.

Modernize Clinical Trials

Opportunity # 34

In December 2007, the FDA and Duke University Medical Center launched a collaboration (Clincal Trial Transformation Initiative, CTTI) aimed at modernizing the way clinical trials are conducted. Under a memorandum of understanding between the organizations, Duke will host a public-private partnership that will include broad representation from government, industry, patient advocacy groups, professional societies, and academia. The participants will work

together to develop new standards and identify new methods and technologies that improve safety, boost the quality of information derived from clinical trials, and make the research process more efficient. Among the ideas that the initiative may explore:

- Establishing national standards for a wide range of research functions to streamline the current approaches to initiating and conducting clinical trials. There is broad agreement that the process is too slow and unnecessarily complicated. Examples could include the development of standardized electronic forms for collecting data as well as standardized contractual agreements that govern the ways in which individual research sites (such as hospitals and physician practices) interact with research sponsors.

- Exploring alternative models for institutional review boards to minimize duplication of effort in multi-site clinical trials and identifying strategies to enhance the process of obtaining informed consent from clinical trial participants.

- Establishing accreditation programs for both clinical investigators and research sites. Currently, research organizations that coordinate large, multi-site clinical trials are required to assess and document the qualifications of each investigator and the quality of each research site participating in a clinical trial. For a large clinical trial the process typically involves several visits to each site, requiring months to complete and often delaying the start of the trial. An accreditation system similar to the one used by hospitals could help research organizations more quickly and efficiently verify the abilities of accredited individuals and sites.

- Extending the use of technology to improve data management. Currently, most of the data collected during clinical trials is recorded on paper. Switching to electronic data management systems would enable researchers to monitor data in real time and help them spot safety problems more quickly. If the electronic systems were standardized across the nation, data from one clinical trial could quickly and easily be compared against data from another.

For more on the initiative, see http://www.fda.gov/oc/initiatives/criticalpath/.

Draft a Guidance on Development of Coronary Drug-Eluting Stents
Opportunity #38

Although under way for some time, this draft guidance was completed during 2007; it issued in early 2008 in time for an April 2008 public meeting. The draft guidance will provide recommendations on the preclinical and clinical studies that should be submitted in support of a marketing application for a coronary drug eluting stent, as well as information about jurisdictional considerations for this drug-device combination product.

Determining Correlates of Protection Against Influenza A in Support Of Pandemic Influenza Vaccine Development
Opportunity #43

A public workshop sponsored by FDA/CBER in cooperation with the National Institutes of Health's Division of Intramural Research within the National Institute of Allergy and Infectious Diseases and the World Health Organization was held on December 10-12, 2007, in Bethesda, Maryland. A group of international experts were convened to identify the gaps in our understanding of pandemic influenza protective immunity, to identify the gaps in our ability to assess pandemic influenza vaccine efficacy, and to propose and develop criteria and procedures to bridge these gaps. The suggestions and recommendations will be incorporated

into a WHO document for pandemic influenza vaccines and should facilitate development of a global research agenda to improve assessment of efficacy for pandemic influenza vaccines.

Requiring Electronic Submission of Study Data and Other Information
Opportunity #44

FDA is considering requiring the electronic submission of all clinical study data submitted for new drug applications, abbreviated new drug applications, biologics licensing applications, and their respective amendments and supplements in a standardized format that FDA can process, review, and archive. This is a crucial step toward streamlining clinical trials through automation of data collection, submission, and analysis. Electronic submission will enable greater use of consensus data standards and pave the way for an array of more efficient data collection and analysis practices for sponsors and investigative sites. At a public meeting on December 18, 2006, FDA solicited input on this plan from potentially affected parties, including the public.

As part of this effort, FDA issued on March 27, 2007, a request for information (RFI) seeking input from the public on the feasibility of creating an *electronic platform* for all regulatory product information that would possibly be developed and managed by a third party. FDA is reviewing received information and exploring next steps. For more see *e-platform* at http://www.fda.gov/oc/initiatives/criticalpath/.

Encourage the Development of Fetal Intrapartum Monitoring Devices
Topic 2: Streamlining Clinical Trials, Advancing Innovative Trial Designs

FDA and NIH's National Institute of Child Health and human Development (NICHD) are planning an Advisory panel meeting for late summer early fall on developing a new paradigm for testing intrapartum fetal monitoring devices. Electronic fetal monitoring (EFM) has been used for decades to help with decision making during clinical management of women in labor. Introduction of EFM technology preceded well-controlled trials establishing efficacy. Even as questions linger about the appropriate use of existing technologies, development of new monitoring technologies continues. However, few new technologies have been submitted to FDA, and one recently approved product has not been integrated into clinical practice. The goal of the workshop will be to identify/differentiate categories of EFM/CAD devices and corresponding levels of evidence; identify appropriate study endpoints and study methods; and discuss possible use of current databases to verify/validate intrapartum EFM/CAD algorithms.

In other medical device fields, progress has been made toward developing an algorithm for studying diagnostic devices. Given the recognized need for better fetal assessment tools, the inconsistency between trial results and clinical acceptance and uncertainties regarding how new fetal monitoring technologies are evaluated, development of a new paradigm for evaluating fetal monitoring devices could stimulate innovation in this field.

TOPIC 3: HARNESSING BIOINFORMATICS

(Several of the topics listed here are relevant to Topic 2.)

Efficient Use of Bioinformatics

Several projects are underway to facilitate the exchange of regulatory product information using an electronic information supply chain.

- **Janus**

  In March 2007, FDA and NIH signed an MOU to establish a formal collaboration between the U.S. Department of Health and Human Services, Food and Drug Administration (FDA) and the U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute (NCI) to create a common standards-based data repository to facilitate the exchange and analysis of study data.

- **FAERS/Medwatch^{Plus} Portal**

  In September 2007, FDA and NIH signed an MOU to develop the rational questionnaire and test the feasibility of a single electronic portal for the submission of pre-and postmarket adverse event/safety reports. A plan was developed and initiated for the integration of both into a single electronic portal under the MedWatch Investment in October. A request for proposal (RFP) for the combined acquisition of FAERS/ Medwatch^{Plus} Portal project was issued in December (a 5-year contract was awarded to SRA International, Inc. in early 2008 for integration of the MedWatch^{Plus} portal and FAERS).

Standardization of Computational Fluid Dynamic (CFD) Techniques Used To Evaluate Performance and Blood Damage Safety in Medical Devices

Opportunity #50

Computational fluid dynamic (CFD) methods for describing flow patterns and fluid forces are increasingly being used in the development and evaluation of blood-contacting medical devices, such as prosthetic heart valves, blood pumps, and oxygenators. Although computer simulations are efficient in creating device designs, there are no standards for the use of these methods to assess performance and safety of the final medical device designs. FDA scientist have begun to standardize computational fluid dynamic techniques used to evaluate performance and blood damage safety in medical devices.

TOPIC 4: MOVING MANUFACTURING INTO THE 21ST CENTURY

Improving Safety Testing for New Cancer Therapies (oncolytic adenovirus)
Opportunity #57

Biologically based drugs need to be tested to ensure that they are free from contaminating viruses; one test is an assay known as the in vitro adventitious assay. However, certain viral cancer therapies are very difficult to test because the product itself kills the cells that are used in the test, resulting in delays in early-phase product development. In 2007, FDA scientists began developing ways to neutralize this problem, thereby enhancing the ability to test these products for safety while reducing the need for sponsors to invest time and money in test method R&D.

Development of Universal Regulatory Strategy for Neurotoxicity Testing of Medical Devices.
Topic 4: Moving Manufacturing Into the 21st Century, Manufacturing Devices

The industry, the professional societies, and the public have been unable to reach consensus on the appropriate amount of neurotoxicity testing needed to access new materials that are used in neurological devices that come in contact with cerebral spinal fluid and neural tissues. FDA currently is examining the data available from literature, available standards, and previous device applications submitted to the FDA to develop an appropriate regulatory strategy, possible standards, and possible guidance to access new materials used in neurological devices.

Develop Instrument Calibration Standards to Encourage Use of Process Analytic Technologies
Opportunity #65

Vibrational spectroscopy and chemical imaging based on near-infrared, mid-infrared, Raman, and terahertz technologies are capable of measuring in-process and finished product attributes. Combining imaging with spectroscopy requires unique standards to ensure proper instrument and data processing operations. One barrier to wide-spread industry adoption of these technologies for continuous quality controlled manufacturing processes is the absence of accepted scientific standards to ensure proper operation of the new instrumentation.

FDA is developing calibration and validation procedures and appropriate instrument qualification standards for use with these new instrumental methods in pharmaceutical research and manufacturing. Standards for Raman chemical imaging have been prepared from polyethylene glycol (PEG) lines on silicon substrates using micromolding in capillaries (MiMIC). The Raman images of these standards were used to determine the impulse response of an imaging instrument by comparing the measured images to model functions of the images. The results provide a quantitative measurement of the influence of light-matter interactions on the spatial resolution achievable with chemical imaging instruments. FDA now plans to work with NIST to produce more rugged targets that can be used in collaborative studies with other laboratories. We have also been optimizing calibration methods to be used for near infra-red quantitative estimation of active pharmaceutical ingredients in the presence of excipients in finished dosage forms. Using data from calibration sets of differing

composition, optimal models are being developed that improve prediction accuracy and show resistance to disturbances from the matrix.

Nanotechnology: Toward Efficient and Predictable Product Development
Opportunity #66

A number of efforts are underway in the field of nanotechnology:

- Under a tripartite MOU (June 2006), FDA, NCI, and NIST have agreed to collaborate and share know-how and data to stimulate innovation through characterization of nanoparticles and standards development.
- FDA is directly involved with the NCI's Nanotechnology Characterization Laboratory (NCL) in the development of characterization assays, preclinical, and early clinical assay development of oncology-based products.
- FDA and NCI have launched Web sites (http://ncl.cancer.gov/ and www.fda.gov/nanotechnology/) for sharing and communicating information and new scientific findings about nanotechnology in real time. Efforts are underway to address scientific and policy concerns and issues for the entire spectrum of products under FDA's jurisdiction. These activities are being conducted under the auspices of the recently established FDA Nanotechnology Task Force and Nanotechnology Interest Group (NTIG), the latter of which comprises review level scientists who are uniquely qualified to provide input on product development.
- A scientific workshop was held March 2008 (http://www.nanohealthalliance.org/fda-anh-nanotechnology-initiative-1) with the Alliance for NanoHealth (ANH) in which a number of senior FDA staff provided scientific and regulatory feedback to the discussions. Goal of the workshop was to identify some of the major hurdles in the pre-clinical, clinical, and manufacturing stages of nanoengineered medical product development. With input from many stakeholders (industry, NIH, academia and FDA), 7 high-priority opportunities were identified that could help speed medical product development in practical and well-defined ways. Some of the priorities set at the workshop include:
    - Define appropriate tools to describe biodistribution and locality of targeted materials over time
    - Develop analytical toolkit for nanopharmaceutical manufacturing (drugs/multicomponent mixtures)
    - Identify imaging techniques that are appropriate for nanotechnology-based materials
    - Identify standard materials that could be used in testing
    - Develop in silico modeling of nanoparticles with biological systems
    - Establish nanomaterial periodic table

Food Processing and Packaging Research
Topic 4: Moving Manufacturing into the 21st Century

The National Center for Food Safety and Technology (NCFST) is a unique food research consortium of the Center for Food Safety and Applied Nutrition (CFSAN), Illinois Institute of Technology, and the food industry. NCFST was established in 1988 to provide a means for university, FDA, and industry scientists to work side-by-side on the development, validation and implementation of food processing and packaging technologies critical for food safety. As a consortium that is in part jointly funded by the university, FDA, and industry, the NCFST has

become a critical resource to FDA for science-based information when developing guidelines and regulations to ensure food safety.

Evidence is mounting on the role of diet in many serious illnesses and chronic conditions. In fall 2007, the NCFST partners launched a new research initiative on "Food for Health." The initiative reflects the realization that often the limiting factors in the *critical path to healthy foods* are the technological barriers that make their production, marketing, and consumption practical. This initiative is using the proven collaborative model between CFSAN and NCFST to examine the role of food technology in the development of foods and food components to improve public health and reduce the health burdens imposed by chronic disease. This work focuses on how technology can be used effectively to help consumers reduce the risk of chronic disease and promote health, while ensuring the safety of food products. Initial work is likely to focus on the relationship between food components and regulation of food intake. The NCFST is currently exploring different means for augmenting its research funding to accelerate this new initiative. A workshop on Health-Promoting Foods is planned for late summer/early fall 2008. A research paper related to the project has recently been drafted and is going through the approval process.

With the FDA's increased interest in the development of good manufacturing practices for drugs, biologics, and devices, the NCFST may offer some unique opportunities for the Critical Path research and development needs for these FDA centers. The NCFST has unique capabilities for conducting pilot-scale industrial operations that may offer other FDA centers a means for addressing critical scientific needs in the area of manufacturing. For example, a BSL-3 facility was completed in early 2008; commissioning and validation of the facility should be completed by 2009. The BL-3 pilot plant/laboratory complex will be the only pilot-scale facility of its kind in the country.

TOPIC 5: DEVELOPING INNOVATIVE APPROACHES TO ADDRESS URGENT PUBLIC HEALTH NEEDS

Detecting Infectious Agent Contamination in Biological Products
Opportunity #57

A number of activities were launched during 2007, including the following:

- FDA scientists are leading a collaboration with NIH, CDC, the U.S. Department of Agriculture, academia (Indiana University School of Medicine, University of Maryland School of Medicine), and industry (American Red Cross, Crucell Holland) in studies to develop and assess technologies for identifying prion (transmissible spongiform encephalopathy, Mad Cow) contamination of biological products. In addition, another project focuses on evaluating candidate diagnostic and blood donor screening tests for prions to protect the nation's blood supply.

- FDA is working to develop and qualify panels of HIV RNA standards and test nucleic acid-based blood donor assays for their ability to adequately detect a variety of new HIV strains from the United States and international locations.

- When blood and tissue transmission of West Nile virus (WNV) was identified, FDA acted rapidly in partnerships with CDC, NIH, and industry to institute experimental testing of blood donors for WNV, thus preventing transmission of WNV to hundreds of blood recipients. Now that WNV blood donor testing is done under FDA license, research collaborations are continuing to understand the incidence of WNV mutations and to ensure the sensitivity and specificity of these blood donor screening tests for WNV mutant viruses.

Microbiological and Molecular Identification of Foodborne Bioagents
Opportunity #67

In 2004, the Center for Food Safety and Applied Nutrition (CFSAN) signed a memorandum of understanding (MOU) with the Department of Homeland Security (National Bioforensic Analysis Center) and the Department of Justice (FBI) to support development of methods that will enable the detection, identification, and tracing of strains of *E. coli, Shigella, Salmonella*, and other foodborne pathogens that could be used in biocrimes or bioterrorist attacks to deliberately contaminate food sources. The goals of this effort serve the needs of (1) food defense, in developing forensics tools that enable the identification and differentiation of individual strains of foodborne bacteria and (2) food safety, in aiding epidemiological efforts to trace strains involved in foodborne disease outbreaks. Since 2004, new technologies have been developed for bioinformatic analysis, DNA microarray, optical mapping, and phenotypic microarray of foodborne pathogens. In 2007, these forensics tools were applied to investigations of the 2006 multi-state outbreaks of *E. coli* O157:H7 linked to spinach and lettuce.

Rapid Pathogen Identification
Opportunity #67

The emergence of antimicrobial resistance in foodborne pathogens due to agricultural antimicrobial use is a public health and drug safety issue.

- FDA's Center for Veterinary Medicine (CVM) is developing rapid test methods (microarray, biomarkers) to screen foodborne pathogens for genetic relatedness and the presence of resistance genes. These tests will help monitor the migration of resistance genes in foodborne pathogens from the animal production environment to humans. The information gained will help assess the risk associated with antimicrobial use in food animal production and development of policy guidelines for their safe use.
- CVM also developed in 2007 the first standardized in vitro test method for antimicrobial susceptibility in *Campylobacter*, a common foodborne pathogen. This standardized test will enhance the effectiveness of surveillance systems for monitoring antimicrobial susceptibility in foodborne pathogens. This test will also help drug sponsors to evaluate the efficacy of prospective antimicrobial drugs for treating *Campylobacter* infections. CVM is currently developing a disk diffusion method for antimicrobial susceptibility testing of Campylobacter.
- The National Antimicrobial Resistance Monitoring System (NARMS) provides continuous collection of data on antimicrobial susceptibility patterns in common foodborne bacteria. This information is used to alert the veterinary medical community and regulatory officials about emerging antimicrobial resistance that may compromise drug efficacy. In addition, NARMS is a powerful source of information that can be used by sponsors in meeting the GFI152 guidelines for review of new animal antimicrobial. NARMS was further strengthened by establishing a DNA fingerprint database of *Salmonella* and *Campylobacter* isolated from retail meats.

  In FY 2007, 1,358 isolates of *Salmonella, E. coli, Campylobacter* and *Bacillus* recovered from food animals, retail meats, and humans were DNA fingerprinted with first restriction enzyme (XbaI/SmaI) using pulsed-field gel electrophoresis (PFGE), and 1,827 isolates were DNA fingerprinted with second enzyme (BlnI/KpnI/NotI). These PFGE profiles have been submitted to CDC's PulseNet program. Currently, CVM has more than 7,000 DNA fingerprint profiles of *Salmonella* (5,100), *E. coli* (379), *Campylobacter* (2565) and *Bacillus* (83) in our database. This database is providing useful information on the epidemiology of multidrug resistant foodborne pathogens.
- CVM also continues to screen feeds and feed commodities for the presence of antimicrobial resistant *Enterococcus* and *E. coli*. This is part of our efforts to investigate issues of importance to animal feed security and support development of the Animal Feed Safety System.

New Small Animal Models for Vaccine Testing
Opportunitiy#70

FDA has been working with Johns Hopkins University School of Medicine to develop and evaluate animal models of human SARS (severe acute respiratory syndrome) infection for their use in preclinical efficacy and safety testing of new candidate SARS vaccines. Findings so far suggest that the ferret may provide a useful model for evaluating SARS vaccine safety and efficacy. Two recent articles describe this model in more detail. See Taylor, D.R., 2006, "Obstacles and advances in SARS vaccine development," *Vaccine* (24:863) and Darnell, M.E.R., Plant, E.P., Watanabe, H., Byrum, R., St. Claire, M., Ward, J.M., and D.R. Taylor, 2007, "Severe acute respiratory syndrome coronavirus infection in vaccinated ferret," *Journal of Infectious Disease* (196:1329).

Development of a Multiclass Veterinary Drug Residue Screening Method
Topic 5: Developing Products to Address Urgent Public Health Needs

Multiclass multi-residue methods for veterinary drugs could be used to speed up development time for sponsor-supplied regulatory methods by serving as a template. Alternatively, they could also serve as the regulatory method. In this case, sponsors could provide a screening method to be used in monitoring programs. Development of a screening test would reduce the burden on industry because a method trial would not be required (an AOAC Research Institute certification should be sufficient). FDA's Center for Veterinary Medicine (CVM) is examining options to make more practical methods available to USDA and industry for screening and monitoring. The primary focus of the multi-residue work in 2007 has been on development of a method for the determination of antimicrobial drugs in honey. The honey matrix is highly variable, due to the wide variety of source plants from which bees harvest nectar and pollen. Because of this inherent variability in the matrix, it is more difficult to develop a robust method. Seventeen antimicrobial drugs have been included in the multi-residue method to date.

FDA (CVM) is also investigating fundamental performance parameters of mass spectrometers when used in residue analysis (matrix suppression effects). Understanding the key factors that affect instrument performance enables better prediction of method transferability. CVM has been able to retrospectively identify several method difficulties that have delayed the approval process. The FDA protocol will enable sponsors to identify hidden performance issues and correct them before submitting the methods to the time and expense of a method trial. In 2007, the research has focused on the effect of varying the amount of sample matrix for quantitative LC/MS analysis. Most methods are developed on the assumption that the amount of sample matrix is constant. However, the amount of sample matrix used in a method can be variable. By studying the error associated with changing the amount of sample matrix in a method, one can establish an acceptable range for sample size.

Animal Models for Veterinary Drugs

Topic 5: Developing Products to Address Urgent Public Health Needs, Better Predictive Disease Models

Approval of drugs in minor species (e.g., zoo animals, ornamental fish, parrots, ferrets, guinea pigs, sheep, goats, catfish, and honeybees) relies on data generated in major species (e.g., dogs, cats, and cows). To support the Minor Use, Minor Species program (MUMS) program, in 2007 FDA's CVM completed the animal phase of a PK/PD study in which we are comparing pharmacokinetics of anti-helminthics used in parasite control in small ruminants (sheep and goats) to cattle. The laboratory analyses of the samples are continuing. CVM also conducted a study to investigate the development of resistance following drug administration in a recirculating aquaculture system. This research will aid in the understanding of the mechanisms of antibiotic resistance to prolong the use of antimicrobial drugs as therapeutic agents and reduce the prevalence of antibiotic resistant bacteria throughout the food production continuum.

Pharmacokinetic/pharmacodynamic studies have also been conducted to evaluate the assumption that pharmacokinetic parameters are unaltered in the diseased state compared to the healthy state for a particular drug/disease/animal species. Initial work suggested that pneumonia may alter the levels of enrofloxacin at the site of infection, as measured in bronchial fluid, an effect that may be different depending on the drug's route of administration. In 2007 the animal phase of a second study using tilmicosin and tulathromycin was completed. The laboratory analyses are ongoing.

In a related effort, CVM scientists used a latex based polymer to map the arteries that supply the posterior aspect of the bovine ear. The ear has become an increasingly common site for the injection of drugs in cattle, primarily to avoid the problem of extended drug residues at the

injection site. Ear injection is also less likely to result in carcass damage and trimming required at slaughter. However, field safety studies with drugs using this route of delivery have resulted in several reports of acute death following administration. These cases have been attributed to inadvertent injection of the drug into an artery, resulting in back-flushing into the cerebral blood supply, leading to embolism and death. Preliminary analysis of the arteries supplying the ear reveals small vessels (1.5-2.5 mm), which narrow substantially as one moves from the base towards the tip of the ear. Scientists were able to trace the ear vessels proximally toward the skull and determine a possible pathway to the brain via the maxillary artery and its branches. However, cattle do not have a functional internal carotid artery, and therefore, back-flush via this pathway is not a possible route to the brain. Scientists are currently using CT scans to enable better visualization of the vascular branching.

New Technology for Detection of Pathogenic Contaminants in Food
Topic 5: Developing Products to Address Urgent Public Health Needs

During 2007, extensive work was done with CRADA partner LITMUS LLC to develop a commercial method for real time detection and enumeration of bacteria in food. The year's accomplishments included formulation of a joint FDA/LITMUS patent on the method and the first on-site implementation trial at a food industry manufacturing plant, Simmons Foods' cook plant in Van Buren (Arkansas) and initiation of development of real time pathogen-specific assays based on fluorescence tagging of target pathogen cells.

OTHER CRITICAL PATH RELATED PROJECTS

New Technology for Measuring Chemical and Microbiological Contaminants

Identifying unknown chemical and microbiological contaminants in regulated food and cosmetic products is a complex, time consuming process. Often, when public health emergencies arise as a result of product contamination, time is a critical element because many food products have short shelf lives (e.g., produce), and we must share critical information with the public as soon as it becomes available. Sound methods are needed to verify the steps taken in any prevention plan, and, given our globalized marketplace, there is a constant demand for faster detection and swift, accurate identification of the type of contamination being dealt with.

FDA is seeking to merge the regulatory requirements of product testing with the private development of new strategies and innovative technologies for detecting and identifying chemical and microbiological contamination. Through partnerships with industry and academia, new tools using the latest developments in science and technology (e.g., nanotechnology, mass spectrometry, optical arrays) are being evaluated and tested for their appropriateness in the rapid identification of contaminated products, the source of product contamination, and the effectiveness of process interventions. Ultimately, these tools will enable faster identification of problems associated with product contamination, resulting in improved public health response.

The Center for Food Safety and Applied Nutrition (CFSAN) has developed several collaborations, for example:

- In 2007, with USDA-ARS and the California Department of Public Health, molecular subtyping of feral E. coli O157:H7 strains geographically and ecologically associated with the Salinas Valley, California, spinach outbreak of 2006
- In 2007, with Michigan State University National Food Safety and Toxicology Center to achieve a better understanding of the emergence of atypical strains of E. coli O157:H7 and relevant genetic factors that distinguish this pathogen from typical E. coli O157:H7;
- In 2006, with The University of Maryland-Department of Nutrition and Food Science on development of novel PFGE-based subtyping schemes for Salmonella, E. coli, and C. botulinum
- In 2007, with The North Carolina State University, College of Veterinary Medicine on the molecular ecology, subtyping and source tracking of feral strains of Salmonella Newport associated with multi-year Tomato outbreaks on the Eastern Shore of Virginia
- In 2007, with the Grocery Manufacturers Association-Food Processors Association (GMA-FPA) and USDA, on investigation of furan formation during irradiation of produce to eliminate pathogens
- In 2007, with FDA's Center for Veterinary Medicine (CVM) and National Center for Toxicological Research (NCTR) on the DNA-sequence analysis and development of alternative subtyping methods for closely related strains of Salmonella Typhimurium, S. Enteritidis, and S. Javiana from poultry sources

- In 2006, with FDA's Center for Biologics Evaluation and Research (CBER) on the characterization of high-invasive strains of Enterobacter sakazakii and the development of an in vitro model for invasion of E.sakazakii using HBMEC brain associated cells

Developing Standards and Processes for Reducing Allergens in Foods

It is estimated that approximately 2 percent of adults and about 5 percent of infants and young children in the United States suffer from food allergies. Adverse reactions associated with food allergies result in roughly 30,000 emergency room visits each year. The Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA) established labeling requirements for foods in an effort to reduce the number of adverse events associated with food allergens. However, to improve compliance with FALCPA and reduce the number of adverse events associated with food allergens, we need to fill some gaps in our knowledge and understanding of food allergens.

Collaborative work in these areas is being conducted through the National Institutes of Standards and Technology (NIST), the National Center for Food Safety and Technology (NCFST: a consortium of FDA, the Illinois Institute of Technology, and industry), and Health Canada. This project will serve to fill these knowledge gaps by

- Development of standards for the major food allergens
- Development of better methods for the detection of allergens in finished products
- Evaluation of strategies for reducing allergens in the manufacturing environment
- Determining the effects of processing on allergencity

Several projects were launched in 2007 under a five-year cooperative agreement including allergen detection methods research, particularly allergen test kit methods; the effects of processing on food allergens; and methods for removal of allergenic foods from food-contact surfaces.

Performing Food Safety Risk Analysis

The Joint Institute for Food Safety and Applied Nutrition (JIFSAN) was established as a collaborative effort of FDA and the University of Maryland, College Park (UMCP) in April 1996. JIFSAN is a jointly administered, multidisciplinary research, education, and outreach partnership that provides opportunities for FDA, UMCP, and members of the food safety community to develop collaborations and leverage resources to address food safety and cosmetic issues. The JIFSAN Cooperative Agreement was renewed for an additional 5 years in September 2007.

JIFSAN advances the use of food safety risk analysis principles to enhance public health, food protection, applied nutrition, and animal health through cooperative research, education, and outreach.

- JIFSAN's FoodRisk.org continues to develop improved tools for user access and searching. These tools include a new user interface and a new search engine that make it easier to find information.
  - In 2007, the site added a number of exclusive data resources, including a new database on consumer food storage practices and information related to produce safety.

  - A collaboration with a visiting scholar from Japan was initiated to develop a prototype of a tool that can extend the search capability of the site from simple keyword matching to mapping of concept relationships. This tool will be available in late 2008.
  - In 2007 JIFSAN began collaborating with the European Food Safety Agency (EFSA) Information Technology Working Group on the development of data exchange standards. This collaborative effort was initiated after the JIFSAN Foodrisk.org Web site was featured in a Web-based presentation as part of the EFSA's September Information Technology Working Group meeting.
- JIFSAN initiated two Risk Communication Research projects. These projects are a collaborative effort between the University of Maryland's Department of Communication and CFSAN's Consumer Research group. The projects are (1) Consumer Survey on the Impact of Perceptions of the 2006 Spinach Recall on Current Spinach Consumption and (2) Increasing the Security of the Food Supply: An Evaluation of the ALERT campaign.

JIFSAN facilitates a variety of interdisciplinary interactions aimed at developing and improving the tools available to risk analysts in areas such as quantitative probabilistic modeling and risk characterization. These interactions are particularly valuable in extending the applicability of risk assessment to new areas (such as food allergens) or for new purposes (such as for comparing public health impacts among different types of hazards). A Tools for Prioritizing Food Safety Concerns Workshop was held in June 2007, bringing together different organizations working on tools for risk screening, ranking, and prioritization to discuss approaches and develop recommendations for a process to prioritize risks associated with chemical and microbial contaminants in food. A white paper is being drafted to report on the workshop findings (see workshop summary at http://www.jifsan.umd.edu/tools_2007.htm).

JIFSAN works with University of Maryland, FDA, other Federal agencies and other partners in the development and implementation of international food safety training programs. Examples of the international training programs include

- The Food Safety Risk Analysis Professional Development program
- Good Agricultural Practices (GAPs) Train-the-Trainer
- Good Aquacultural Practices (GAqPs) Train-the-Trainer

In 2007, JIFSAN established an industry consortia that began working with University of Maryland's Department of Nutrition and Food Science to further the development of a Commercially Sterile Packaged Food (CSPF) training program for inclusion into the JIFSAN International Training portfolio. A comprehensive CSPF Training Manual is currently being developed.

Using Science for Authentication and Analysis of Botanical Dietary Supplements

The cooperative agreement between CFSAN and the University of Mississippi's Thad Cochran National Center for Natural Products Research (UM-NCNPR) was established to assist FDA with implementation of the Dietary Supplement Health & Education Act of 1994 (DSHEA). This partnership enables a more efficient use of research resources to identify and analyze specific components in ingredients, including botanical ingredients, thereby ensuring that dietary supplements are safe and their labeling is truthful and not misleading. Additionally, the collaboration provides opportunities for addressing problems associated with natural products through research.

One piece of this program involves identifying and developing unique laboratory approaches for assessing the safety of new botanical dietary ingredients. Although botanical supplements are widely available in retail outlets, supplements are usually complex mixtures that make it difficult to properly assess the safety of specific botanical ingredients. Therefore, it is essential that authentic, botanically correct reference materials and chemical standards for these botanicals are readily available to the Agency. Obtaining these authenticated botanicals had been difficult prior to this agreement. These reference materials and standards form the basis of the development of analytical methods, the conduct of toxicological studies, and the development of regulatory enforcement strategies.

The collaborative partnership between FDA and the UM-NCNPR strongly encourages the development of projects with external partners that build on the activities supported by the cooperative agreement. In 2007, UM-NCNPR continued to build collaborations that extend beyond the U.S. boarders.

- The Sino-U.S. Traditional Chinese Medicine (TCM) Research Center was established in April 2007 and is jointly located at UM-NCNPR in the School of Pharmacy and at the Shanghai Institute of Materia Medica (SIMM), Chinese Academy of Science in China. The mission of the Center is to bring the science on the forefront and provide scientific evidence to traditional medicine.
- A research program was initiated in late 2007 at SIMM entitled Quality Control and Toxicity Research of Traditional Chinese Medicines Used Commonly in the United States. Projects focus on the efficacy and safety of Rhizoma Arisaematis, Radix Bupleuri, and Rhizoma Pinellia). These plants were identified by UM-NCNPR after discussions with CDER. They are used traditionally with a specific method of preparation but if they are extracted differently some safety issues may result when using the new product. Related species, distribution, actions/indications, adulterants, chemical constituents from the literature, compound isolates and cytotoxicity results were reviewed. Collaborators include representatives of the Natural Products Chemistry Department, SIMM, the Shanghai Research Center for Modernization of Traditional Chinese Medicine, SIMM, and the Second Medical Military University. Funding for this research has been provided by the Chinese state and local governments.

CARVER + Shock Software Tool for Food Defense

During the fall of 2005, FDA contracted with the Institute of Food Technologists (IFT) and Sandia National Laboratories (SNL) to develop a software tool that will enable this defense methodology to be applied to food production. The CARVER+ Shock Vulnerability Assessment software, developed by Sandia Labs for FDA, enables the user to think like an attacker by identifying the most vulnerable targets. With the help of the software tool we are developing, the food industry will be able to focus its resources and protection measures on the most vulnerable points in their food production and transportation processes, thus helping to protect the nation's food supply. The CARVER + Shock program has the ability to generate customized results that are applicable to the food production of individual facilities and firms. The purpose of this project is to develop the CARVER + Shock methodology into a set of detailed inquiries that can then be inserted into an existing software screening tool for evaluating potential threats of chemical, biological, or radiological contamination within the food industry from deliberate acts.

CFSAN began making this software tool available free beginning June 2007 through CFSAN's Food Defense and Terrorism Web page (www.cfsan.fda.gov/fooddefense). The tool has been developed with the assistance of an advisory team consisting of seven respected experts in the

food safety or defense field. The project will initially refine, optimize, and computerize the CARVER + Shock security methodology.

Collaboration between FDA and the University System of Maryland (USM)

Although the FDA is working with a number of academic institutions on a variety of projects related to its mission, FDA has established a particularly broad-based collaborative effort with the University System of Maryland. In 2007, FDA and USM signed a memorandum of understanding (MOU) (http://www.fda.gov/oc/mous/academic/225-07-8405.html) that establishes terms of collaboration between FDA and USM to support a variety of programs including collaborative research, public outreach, extension activities, cooperative international initiatives, disciplinary training, and exchange of scientists and staff, including sabbaticals, postdoctoral fellowships, and student internships.