

Critical Path Opportunities Initiated During 2006

In March 2006, FDA published the second of two reports on the Critical Path to medical product development, *Critical Path Opportunities Report and List*. The *Opportunities Report and List* presented 76 specific scientific opportunities that, if undertaken, would help modernize the Critical Path sciences. The opportunities were identified through extensive outreach with patient groups, the pharmaceutical industry, academia, other federal agencies, and other health related organizations

FDA also promised in that report to announce the specific activities it was undertaking in support of its Critical Path Initiative. As promised, the following pages list more than 40 Critical Path collaborations and research activities that currently are underway with FDA participation. The activities are organized according to the priority topics discussed in the *Opportunities Report and List*, also available on the Critical Path Web page.¹ Where appropriate, an activity is designated as directly linked to one of the 76 specific scientific opportunities,² or priority topics, in the *Opportunities Report and List*. The priority topics include the following:

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

We realize that for many of these activities, our work will only be a first step in overcoming a Critical Path hurdle, and we and others will have to build on the results of these first steps.

For most projects, the timing of deliverables will depend 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 depend on the availability of our partners' resources. As a result, firm timelines cannot be predicted. In all cases, however, these activities will help increase efficiency, predictability, and productivity in the development of new medical products with the goal of getting promising new products to patients sooner.

As projects are completed and new activities begin, we plan to update this list.

¹ See <http://www.fda.gov/oc/initiatives/criticalpath/>.

² Although only one opportunity is listed for each activity, in some cases, an activity relates to more than one opportunity.

TOPIC 1: BETTER EVALUATION TOOLS

Develop a Concept Paper on Biomarker Qualification

Opportunity #1

This concept paper will be the Agency's first public statement on clarifying the nature and amount of evidence we will be looking for to support a variety of regulatory uses for biomarkers during medical product development. Today, the term *biomarker* is used in many different ways; this paper will present a conceptual framework to facilitate a common understanding and common vocabulary for different biomarker qualifications and uses. We are preparing this concept paper as a first step toward drafting a guidance on this and related issues. Once we have received public input on the concept paper, we will move forward with the draft guidance.

Improve Dosing of Warfarin

Opportunity #1

FDA is collaborating with the Critical Path Institute (C-Path) and the University of Utah on the Cardiovascular Drug Safety and Biomarker Research Program (<http://www.fda.gov/oc/initiatives/criticalpath/biomarker.html>) to establish an evidence-based framework for determining the clinical utility of cardiovascular biomarkers, including genetic variants that determine the anticoagulation response to warfarin. There is wide inter-individual variation for this drug that may lead to severe consequences of under- or over-dosing. A pharmacogenetic algorithm may improve the therapeutic efficacy and safety of warfarin dosing. FDA is involved in a project sponsored by the National Heart, Lung, and Blood Institute (NHLBI) and other thought-leaders in the field to agree on (1) specific elements of clinical trial design; (2) which dosing algorithms to evaluate; (3) how other factors such as age, gender, and weight might influence patient response to warfarin; (4) patient enrollment; (5) what single nucleotide polymorphisms (SNPs) to measure; (6) how the in vitro diagnostic and clinical data might be collected, analyzed, and shared; and (7) what information would facilitate development of new genetic diagnostic tests for specific genotype-based dosing and drug-label recommendations.

Pharmacogenomic Biomarkers for Immune Responses to Hemophilia Therapy

Opportunity #1

Human Factor IX is used to treat hemophilia. Using animal models, FDA staff have identified genes that control antibody responses to factor IX. Studies with the National Institutes of Health (NIH), academia, and industry partners are underway using this information to evaluate the association of these pharmacogenetic markers in humans who have experienced undesired outcomes following treatment with blood products for hemophilia. We hope to also identify possible value for these genetic markers for developing personalized medicine approaches for treating this life-threatening disease.

Draft Drug-Diagnostic Co-Development Guidance

Opportunity #1

This guidance will explain how to co-develop a drug or biological therapy and testing device in a scientifically robust and efficient way. Drug/test combinations have the potential to provide clinical benefits to patients (e.g., differential diagnosis of a disorder, identification of patient subsets, identification of a potential responder, way to target therapy, approach to

identifying individuals at risk for adverse events, monitoring response to drugs, individualizing therapy). A concept paper on the topic — discussing design and statistical considerations to apply to both biomarkers and drugs developed for use with biomarkers — was made public in April 2005 for discussion at a collaborative workshop on related issues. FDA received numerous useful comments at both the workshop and in an FDA Docket and is developing a draft guidance using this input. The concept paper is available on FDA's Web site at <http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf>.

Developing and Testing Calibration Standards for Instrument Validation and Quantification of Multi-Color Flow Cytometry

Opportunity #1

Flow cytometry data are needed to support many clinical; pharmacologic/toxicologic; and chemistry, manufacturing, and controls (CMC) approaches used in drug, device, and biologics product development and approval. One barrier to the development of cancer therapies and diagnostics is the need for flow cytometric measurements to be reproducible across laboratories during clinical trials. Standards are needed to demonstrate comparability between laboratories and across different instrument platforms, specifically, (1) validation of instrument performance in flow cytometry measurements and (2) standards for quantitation of multicolor cytometer measurements. Several Federal and private partners are discussing collaborative approaches to the assessment and certification of fluorescent standard microbeads, including FDA, the National Institute of Standards and Technology (NIST), the Centers for Disease Control and Prevention (CDC), the Environmental Protection Agency (EPA), NIH, BD Bioscience-Pharmagen, Beckman-Coulter, Cytomation-Dako, InVitrogen, Duke Scientific Spherotech, the International Society of Cytometry (ISAC), and the Clinical Cytometry Society (CCS).

Tests for Measuring HIV Vaccine Efficacy

Opportunity #1

Determining the efficacy of HIV vaccines can be difficult because the currently licensed HIV blood test does not differentiate between antibodies developed in response to the vaccine (supporting efficacy) and actual infection with HIV (which would show lack of vaccine efficacy). FDA scientists, working with the NIH, academia, and industry scientists, are developing and evaluating a rapid assay that could be able to distinguish antibodies generated to the vaccine from antibodies due to failure of the vaccine and infection with HIV.

Develop New Ways to Evaluate Potential Toxicity of Complex Biological Products

Opportunity #1

Complex biological products, such as gene vectors, are not amenable to standard toxicology studies. The National Toxicology Program (NTP) is an Department of Health and Human Services (HHS) collaboration between the FDA and the National Institute of Environmental Health Sciences (NIEHS). Through the NTP process, FDA is developing new toxicology methods for studying and licensing safe biological products. For example, the NTP is now launching its first formal, large-scale evaluation of a new animal model for predicting gene therapy vector toxicity in a collaboration with academic partners.

Examine Genetic Basis of Adverse Events

Topic 1: Better Evaluation Tools, Safety Biomarkers

The FDA is in discussion with several NIH institutes and other entities about the applied research that is needed to elucidate the genetic basis of drug-induced adverse events. By leveraging resources, such as FDA's Adverse Events Reports database and other databases containing information on drug-related adverse events, a number of relevant issues in this area can be addressed and processes established, for example, related to sample/data collection, annotation, archiving, and analysis; improving safety profiles of compounds in preclinical and clinical development and drugs in the marketplace; and establishing resource networks for use by all stakeholders. A NIH-FDA workshop on the Genetic Basis of Adverse Drug Reactions was held December 11 and 12, 2006.

A new consortium, the Severe Adverse Events (SAEs) Consortium, being established by the Pharmaceutical Biomedical Research Consortium (PBRC), will work on developing the patient/sample networks and related research programs required to understand the genetic basis of drug induced SAEs. The SAEs Consortium will attempt to improve the safety profile of compounds in preclinical and clinical development and drugs in the marketplace. FDA is acting in a scientific advisory role to this SAEs consortium.

Broaden Our Understanding of Drug-Induced Liver Injury

Topic 1: Better Evaluation Tools, Safety Biomarkers

FDA is working with industry, academia, and other experts to broaden our understanding of the biochemical and genetic bases of drug-induced liver injury (DILI). FDA co-sponsored a scientific workshop (June 2006) to determine the feasibility of developing an in-silico model for DILI from which other predictive experimental models can be derived to characterize potential hepatotoxicity. The long-term goal is to collaborate with experts in the field to develop a model, or models, that can help researchers identify appropriate criteria for determining when early clinical intervention is appropriate. It is also hoped that predictive bioassays and biomarkers can be identified that will help determine which patients most likely will suffer liver toxicity from specific compounds.

Participate in Microarray Standards Developing Consortia

Opportunity #2

FDA is participating in several consortia that are developing voluntary consensus standards to enable the application of microarray technologies to drug development and regulatory decision making.

- FDA was instrumental in creating the ***Microarray Quality Control (MAQC) Project Consortium***, which is developing proficiency and analysis standards for laboratory hybridization methods. These standards will allow laboratories to assess their proficiency at microarray experimentation. Other MAQC participants include equipment suppliers and suppliers of RNA samples. (The results of the MAQC collaboration were published in the September 8, 2006, special issue of *Nature Biotechnology* <http://www.nature.com/nbt/focus/maqc/index.html>.) Consortium work continued with the publication in the *Federal Register* on April 21, 2006, of a solicitation for gene expression datasets from hybridization studies and for statisticians interested in their analysis. These datasets and statistical analyses will allow a comprehensive evaluation of conclusions from the original MAQC collaboration, as well as a survey of other data analysis protocols in use today.

- The **External RNA Controls Consortium (ERCC)** is developing standards for several steps in microarray experimentation, including for oligonucleotide sequences (so-called *spikes*) that will allow data to be compared across experiments and standards on how to read and interpret data from these experiments. FDA is one of many participants. The ERCC is currently testing the standards developed through this collaboration.

Develop Efficacy Surrogates for Cardiac Drug-Eluting Stent Trials

Opportunity #6

FDA has initiated a variety of activities to improve our understanding of how to measure and predict the efficacy of drug-eluting stents. FDA, AdvaMed, and academic researchers are examining angiographic outcomes (in particular, late loss in lumen diameter) to determine whether they can be used as surrogates for clinical outcomes, such as myocardial infarction, death, or the need for repeat vascularization procedures, in evaluating drug-eluting stents. We are also exploring predictive modeling approaches. This work includes evaluating statistical models for validating proposed surrogate measures to facilitate the development of these products and to broaden our understanding of their long-term effects. Under the umbrella of the recently launched (September 2006) Cardiovascular Safety and Research Consortium (<http://www.fda.gov/bbs/topics/NEWS/2006/NEW01467.html> and www.cardiac-safety.org), FDA is in early-stage discussion with multiple partners on 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 late stent thrombosis and bleeding events.

Predicting Mumps Vaccine Efficacy

Opportunity #8

FDA scientists are working with the CDC to identify specific vaccine efficacy questions surrounding the largest U. S. mumps epidemic in 20 years. Critical path challenges that are being evaluated include confirming the ability of the currently licensed vaccine strain to protect against changes in the circulating wild-type mumps virus strain, evaluating the minimum antibody response to vaccine that is protective against mumps, and identifying the best methods for evaluating vaccine responses. This information and these scientific tools will be important in the evaluation of new mumps vaccines in the future.

Predicting the Safety and Efficacy of Malaria and Leishmania Vaccines

Opportunity #8

In animal models, FDA scientists are evaluating genetic markers that affect the responses to immunization with subunit or live, attenuated malaria, and leishmania³ vaccines to help predict the vaccine responses in patients in clinical studies. In addition, vaccine biomarkers are being evaluated to predict the stability and safety of these vaccines.

Qualify Oncology Biomarkers

Opportunity #12

In January 2006, the FDA, the National Cancer Institute (NCI), and the Centers for Medicare and Medicaid Services (CMS) executed an MOU for the Oncology Biomarker Qualification Initiative (OBQI), thereby creating a framework for collaboration to qualify cancer biomarkers that can be useful in research, developing diagnostic tests, medical product

³ Leishmaniasis is a parasitic disease spread by the bite of infected sand flies. There are several different forms of leishmaniasis. The most common forms are *cutaneous leishmaniasis*, which causes skin sores, and *visceral leishmaniasis*, which affect some of the internal organs of the body (e.g., spleen, liver, bone marrow).

quality assessment, and evidence-based decision-making. This collaboration focuses on four key areas: (1) cancer imaging; (2) molecular diagnostic assays and targeted therapies; (3) clinical trials; and (4) data mining.

Two initial projects in cancer imaging (Non-Hodgkin's Lymphoma and Non Small Cell Lung Carcinoma) will develop new and/or revised composite criteria for using FDG-PET imaging in assessing response to therapy. For the FDG-PET in NHL study, additional FDG-PET scans will be added to an existing NCI Non-Hodgkin's Lymphoma trial (reducing the overall costs by not having to start a new trial) with the goal of assessing the clinical utility and advantages of this imaging modality in evaluating patient response to a given therapy. In the second study, the goal is to test whether quantitative changes in FDG uptake during chemotherapy can provide an early readout for the effectiveness of therapy in patients with advanced NSCLC. This will lay the foundation for quantitative FDG-PET as a potential biomarker for drug development. Both studies will be supplemented with private funding to NCI through The Biomarkers Consortium (see below).

Biomarker Development and Qualification

Opportunity #1

To facilitate the search for and clinical qualification of biomarkers, The Biomarkers Consortium was launched in October 2006. This Consortium is a public-private biomedical research partnership supported by the Foundation for the National Institutes of Health, Inc. (FNIH). It involves a variety of public and private stakeholders, including the NIH; FDA; CMS; the pharmaceutical, biotechnology, diagnostics, and medical device industries; non-profit organizations and associations; and advocacy groups. It is the goal of The Biomarkers Consortium to accelerate the delivery of successful new technologies, medicines, and therapies for prevention, early detection, diagnosis, and treatment of various diseases. The first set of projects approved for funding and implementation under The Biomarkers Consortium include:

- FDG-PET in NHL and in NSCLC (see previous activity)
- Whole Genome Association in Major Depressive Disorder: Identifying Genomic Biomarkers for Treatment Response
- Diabetes and Pre-Diabetes Biomarker Project
- Evaluate the Utility of Adiponectin as a Biomarker Predictive of Glycemic Efficacy by Pooling Existing Clinical Trial Data from Previously Conducted Studies

Identifying Viral Genomic Markers Predicting Vaccine Neurotoxicity

Opportunity #16

Using an animal model developed at FDA, our scientists are leading an international consortium with the World Health Organization to develop improved neurotoxicity predictive assays for live viral vaccines. Efforts are underway to link specific genomic changes and virus strain population ratios with increased or decreased safety outcomes in the nervous system.

Identify Indicators of Cardiac Toxicity: ECG Warehouse

Opportunity #18

FDA partnered with Mortara Instruments Inc., under a Cooperative Research and Development Agreement (CRADA) to design and build a warehouse to hold digital electrocardiograms (ECGs) used for drug approval; the warehouse now contains more than 400,000 ECGs. This database will facilitate regulatory review and research and aid in the

development of evaluative tools that can be used in drug development and clinical decision making. In a second phase to this effort, FDA and the Duke Clinical Research Institute (DCRI) have founded a collaborative consortium: the Cardiovascular Safety and Research Consortium (<http://www.fda.gov/bbs/topics/NEWS/2006/NEW01467.html> and www.cardiac-safety.org) with members of academia, patient advocacy, other government and non-profits, and industry partners to coordinate and support a variety of research projects involving the ECG warehouse, as well as other resources obtained in clinical trials evaluating drug effects on cardiac repolarization. Specific projects will look for more reliable means to measure drug effects on the QT interval of the ECG, establish norms, and develop more sensitive assays for repolarization effects. These activities were discussed preliminarily at the Cardiac Safety and Critical Path Initiative Think Tank meeting in October 2005, at a DIA meeting in May 2006, and at a workshop in November 2006.

Predictive Safety Testing

Opportunity #20

The Predictive Safety Testing Consortium (PSTC) was officially launched in March 2006. FDA is providing scientific and strategic input to this collaboration between the C-Path Institute and 15 pharmaceutical industry partners to validate preclinical (genomic) biomarkers of toxicity to use as experimental systems to test for the possibility of toxicity in humans. A particularly innovative aspect of this consortium will be the sharing of biomarkers for cross evaluation by other members of the consortium. These companies have agreed to share data about preclinical and clinical genomic, proteomic and metabolomic biomarkers of drug-induced nephrotoxicity, hepatotoxicity, vascular injury, and genotoxic and nongenotoxic carcinogenicity. These data will be combined with prospective studies as needed to generate biomarker qualification packages for evaluation by the FDA.

Modernizing Predictive Toxicology: Developing Better Tests for Predicting Blood Vessel Damage Due to Infections or Biological Product Use

Opportunity #20

Complex biological products are designed either to protect from infectious agents that cause serious shock caused by blood vessel toxicity (e.g., vaccines for anthrax) or may have direct adverse effects on the blood vessels (e.g., hemoglobin based oxygen carriers (HBOC)). FDA is working to develop and evaluate an in vitro model of blood vessels for testing both the efficacy of anthrax vaccines and to evaluate and predict the risk for adverse events due to HBOC.

Predict Drug Effects on Kidney Function

Opportunity #20

FDA and Novartis are collaborating, via a CRADA, on the identification of nephrotoxic biomarkers that predict the effects of drug compounds on kidney function. Knowledge and experience gained from this collaboration will be used to help pilot a preclinical genomic biomarker qualification process. These activities are also linked to the Predictive Safety Testing Consortium activities mentioned above.

Develop Standard Protocols for the Use of Imaging Techniques During Clinical Trials

Opportunity #22

FDA is participating in a unique collaboration of professional associations (in particular, the American College of Radiology and the Society of Nuclear Medicine), the CMS, and industry to develop standard protocols for the use of imaging techniques during clinical trials. Although FDA is a key participant, the professional associations are responsible for developing the protocols. The associations will obtain input from government and industry participants and post the final protocols on a Web site, making them available free of charge. The goal of this novel collaboration is to facilitate the comparison of images within and across clinical trials as well as the compilation of the data needed to demonstrate that a particular technique predicts the clinical course sufficiently for use as a biomarker. The need for such an effort was identified at the May 2005 Workshop (Use of Medical Imaging As A Drug Development Tool: An FDA/DIA/BIO Workshop; see <http://www.fda.gov/cder/regulatory/medImaging/default.htm>).

Develop New Models for Predicting the Safety and Effectiveness of Emerging Therapies for the Treatment of Vascular Stenosis and Restenosis

Opportunity #30

FDA has begun a long-term project to develop new tools for predictive preclinical evaluation of the safety and effectiveness of emerging therapies (including novel delivery mechanisms) for the treatment of vascular stenosis and restenosis. Our long-term goal is development of more predictive preclinical animal models and FDA recommendations (including performance standards) for evaluating novel interventions and combination technologies to treat vascular disease. We hope to develop serial sampling methods that can provide preclinical pharmacokinetics and pharmacodynamics data that currently are unavailable for emerging therapies and to develop imaging tools that can provide more informative data from animal studies.

Develop Better Animal Models for Predicting the Effects of Compounds Released from Medical Devices on Compromised Hosts

Opportunity #32

FDA has begun a long-term research effort to develop clinically relevant animal models, beginning with animal models of renal failure and sepsis, to better assess the effects of compounds that may leach from medical devices on critically ill patients. This work includes the identification and measurement of biomarkers to predict these effects.

TOPIC 2: STREAMLINING CLINICAL TRIALS

Develop Guidances on Advanced Clinical Trial Design

Opportunity #34

FDA has begun work to facilitate innovation in aspects of study design and analysis related to using multiple endpoints, adaptive trial and enrichment designs, non-inferiority trial designs, and handling missing data. FDA plans to develop concept papers/guidances addressing these issues. In addition, PhRMA organized a 2-day workshop on November 13-14, 2006, to discuss adaptive trial designs.

Draft a Guidance on Development of Coronary Drug-Eluting Stents

Opportunity #38

This 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.

Propose Regulations to Require Electronic Submission of Study Data

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. A public meeting is scheduled for December 18, 2006, to solicit input on this plan from potentially affected parties, including the public.

Streamlining Clinical Trial Data Collection

Opportunity #45

Private efforts to streamline clinical trial data collection through voluntary standardization of case report forms (CRFs) have recently been formalized under the auspices of the Clinical Data Acquisition Standards Harmonization (CDASH) Initiative. Catalyzed by the Clinical Data Interchange Standards Consortium and the Association of Contract Research Organizations, dozens of product sponsors, investigators, data managers and other stakeholders are working together to agree on a core set of data collection fields to support clinical research studies (i.e., creation of consensus CRFs and implementation guides for four "safety data/domains": adverse events, prior medications, concomitant medications, demographics and subject characteristics). FDA is providing input on issues as requested (e.g., FDA requirements). The CDASH process is open to any participant and will include a public comment process (see www.cdisc.org).

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 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 advisory panel previously recommended additional evaluation of a second recently submitted product.

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.

Electronic Drug Registration and Listing

Topic 2: Streamlining Clinical Trials, Advancing Innovative Trial Designs

FDA has proposed new regulations (August 23, 2006) that would require companies to register their firms and list their drug products with FDA electronically, making the process more efficient for both industry and FDA. The electronic registration system will automate firm registration; the electronic drug listing system will automate the maintenance of the United States drug product inventory and help ensure the accuracy of the publicly accessible National Drug Code Directory. (*National Drug Codes are used to uniquely identify all drug products and are widely used in pharmacy dispensing, as well as in labeling and reimbursement systems.*) Over time, the standardized product labeling process (announced in October 2005⁴) and the electronic listing process will be integrated to reduce the burden on industry and ensure the accuracy of this information while providing the most useful real-time information to the public.

Federal Investigator Registry for Biomedical Information Research Data (FIREBIRD)

Topic 2: Streamlining Clinical Trials, Streamlining and Automating Clinical Trials

The FDA and NCI (National Cancer Institute) are working to enable NCI clinical investigators, NCI, and FDA to manage NCI's clinical investigator information online in a fully secure manner. NCI and FDA have established (August 2006) a formal collaboration through a memorandum of understanding to accomplish this goal. FIREBIRD will be the first of several components of a larger NCI-FDA effort underway to enhance the exchange of clinical research information among NCI, its investigators and grantees, and the FDA.

TOPIC 3: HARNESSING BIOINFORMATICS

Develop Tools to Predict Performance of Cardiovascular Stent Prototypes

Opportunity #50

FDA is providing scientific and regulatory expertise to an industry consortium coordinated jointly by Stanford University and SRI International to develop computer models of adult and pediatric cardiac vascular structures and software algorithms to predict the performance of implanted stents. The goal is development of open source tools to predict the performance of multiple alternative stent designs prior to fabrication, animal testing, and human trials. Another goal is development of standard engineering test methods to look at the mechanical fatigue life of stents using clinically relevant loading conditions.

Improve Designs of Late Stage Clinical Testing

Opportunity #51

Late phase trials are thought to have a high failure rate, in part, for predictable reasons, such as nonoptimal dose selection. The FDA has started a voluntary program of engaging sponsors after their phase 2A trials to use clinical trial simulations to help them improve

⁴ Beginning in October 2005, FDA is accepting electronic submission of the content of labeling for all prescription products using the structured product labeling (SPL) format. SPL is a Health Level Seven (HL7) standard that will allow the FDA to make its most up-to-date medical product information available to the public free of charge on the Internet using the National Library of Medicines DailyMed Web site.

dose selection for phase 2B and phase 3 studies. Upon sponsor request, the sponsor and FDA scientists conduct trial simulations using information on the drug (from the sponsor's preclinical, phase 1, and phase 2A data), the disease biomarker and primary endpoint time-course and variability (from publications), and prior clinical trial information (e.g., dropout rates, placebo effect, adherence). The resulting quantitative analyses form the basis for an "end of phase 2A meeting," a scientific interchange without binding agreements intended to increase late-phase clinical development productivity.

Topic 4: Moving Manufacturing into the 21st Century

Improving Manufacture of Influenza and Other Vaccines *Opportunity #54*

Several efforts are underway:

- **Preparing for Pandemic Influenza Vaccine**

The FDA is preparing libraries of possible pandemic influenza virus strains for rapid dissemination to manufacturers for vaccine standards, preparing tests for determining vaccine potency and efficacy, and developing and evaluating better test methods to optimize moving manufacture of vaccine from egg-based systems to cell culture substrates.

- **Predicting Safe Cell Substrates for Vaccine Production**

FDA, in collaboration with the National Institutes of Allergy and Infectious Diseases (NIAID) is developing streamlined, 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. This work will facilitate evaluating the safety and quality of cell cultures proposed for use in influenza vaccine production and new vaccines developed to counter terrorism threats. These issues and the next steps in assessing the safety of cell-based substrates were discussed at a conference in November 2005, funded by the National Institute of Allergy and Infectious Diseases (NIAID).

- **Manufacturing Innovations Supporting Clinical Trials of Vaccines for Global Public Health**

FDA is engaged in initiatives to bring safe vaccines to developing countries and to aid the development of the next generation of tuberculosis (TB) vaccines. With the Program for Appropriate Technology in Health (<http://www.path.org/>), FDA is working to apply FDA technology to the production of low-cost, safe, and effective meningococcal vaccines. The first target area is sub-Saharan Africa where recurring meningitis outbreaks cause high mortality in infants and young adults. With the Aeras Global TB Vaccine Foundation (<http://www.aeras.org/about/index.html>), FDA is developing FDA technologies and methods for use by vaccine developers and regulatory agencies in determining whether

new TB vaccine candidates are safe for use in persons previously infected with TB. Both these initiatives, and many others, will make significant contributions to the global public health.

Improve Use of Imaging in Characterizing and Standardizing Biological Products

Opportunity #56:

Several efforts are underway:

- **Using Advanced Technologies for Characterizing and Standardizing Complex Biological Products**

FDA is exploring how to adapt high-tech imaging methods (e.g., nuclear magnetic resonance spectroscopy and mass spectroscopy) to better characterize complicated biological products, including glycoprotein vaccines for pneumonia and meningitis, influenza vaccines, and allergen extracts.

- **Using Genomic Microarrays to Assess the Quality of Cell Substrates Used to Manufacture Biological Products**

Currently, few predictive methods exist to monitor the quality of cells used to manufacture vaccines, protein drugs, and gene vectors. In collaboration with the NIH and other partners, new microarray technologies and other tools are being developed and evaluated to predict the quality of cell substrates. Discovery of specific gene expression patterns or identification of clusters of specific genes will help characterize cell substrates and may serve as biomarkers of manufacturing quality.

Establish Standards for Novel Forms of Drug Delivery

Opportunity #64

FDA is engaged in a variety of activities to help establish standards for sponsors interested in developing novel dosage forms for drug delivery, including the following:

- **Nasally Inhaled Products**

Today there is no standard reference method for assessing the distribution of active pharmaceutical ingredient (API) particle size in nasal spray suspensions. In addition, there is inconsistency in measurements of particle sizes between micronized and formulated API and variability in particle sizes upon repeat measurements. Raman chemical imaging (RCI) appears to have potential as a method for establishing the chemical identity, particle size, and distribution characteristics of APIs in aqueous suspension nasal sprays, but more analytical work is necessary to fully develop and validate its use. FDA is working to refine RCI use in aqueous nasally inhaled products. If successful, the method will later be applied to other product types, such as dry powder inhalers and metered dose inhalers. The goal is to develop accepted scientific standards for key characteristics of these products, so sponsors will have greater certainty regarding acceptable product parameters.

- **Transdermal Drug Delivery Systems**

FDA is developing methods (e.g., peel, tack, and shear) to assess adhesive properties. In vitro methods are also being developed to compare drug diffusion and skin

permeation of different transdermal systems. Methods developed through this work will form the basis for FDA guidance, possibly, ASTM⁵ standards for these products.

- **Characterization of Liposomal Drug Products**

Building on prior FDA work to develop methods to characterize liposomal drug products (e.g., encapsulation efficiency, leakage, particle size) and their performance under a variety of physiologic stress factors (e.g., thermal, oxidative, acidic, basic), in 2006 FDA hopes to develop an in vitro cell line bioassay method to assess changes in liposomes.

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. FDA is partnering with instrument manufacturers and pharmaceutical firms for collaborative development and testing of validation reference systems. For each method, our goal is to specify both a suitable set of material samples and a corresponding set of specifications determined by a common statistical procedure. FDA plans to develop a draft guidance on the standards for public comment.

Characterization of Nanotechnology Particles

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.

⁵ American Society for Testing and Materials

Use of Nanotechnology to Increase Speed and Sensitivity of In Vivo and In Vitro Diagnostics for Blood Borne Infectious Contaminants and Product Quality

Opportunity #66

FDA scientists are studying how to apply novel technological approaches to determining the purity of biological products, including blood and blood products. Using a nanotechnology based approach, a study is underway to evaluate the sensitivity and specificity of new methods of detecting biological product contamination, in collaboration with academia (Northwestern University) and industry (Nanosphere, Inc.).

Pharmaceutical Manufacturing Using Quality by Design and Process Analytical Technology (PAT) for Monitoring Quality Assurance

Topic 4: Moving Manufacturing into the 21st Century

FDA is working with Novartis to develop a case study of a quality-by-design approach to manufacturing drug substance and drug product. This approach identifies critical processing variables (environmental and process factors, raw materials attributes) and systematically determines their effect on performance and quality. The goal is development of new manufacturing approaches that improve sponsors' ability to assess and improve product quality. PAT tools (e.g., near-infrared and Raman spectroscopy and chemical imaging) are being developed to monitor critical manufacturing steps to provide quality assurance and to interface with process control.

TOPIC 5: DEVELOPING PRODUCTS TO ADDRESS URGENT PUBLIC HEALTH NEEDS

Detecting Infectious Agent Contamination in Biological Products

Opportunity #57

A number of activities are underway, 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.
- Many people are unable to donate blood because they have traveled through malaria endemic areas. Although it is likely few of these individuals are infected with transmissible malaria parasites, there is currently no FDA-licensed blood donor screening test for malaria. New blood donor tests are being developed and

evaluated by FDA for their ability to sensitively and specifically detect malaria parasites.

- 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.

New Small Animal Models for Vaccine Testing

Opportunity#70

FDA is 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.

TOPIC 6: SPECIFIC AT-RISK POPULATIONS — PEDIATRICS

Develop Pediatric Trials Database

Opportunity #72

The goal of the Pediatric Trial Database Development and Analysis Project is to improve the success rate and accelerate pediatric drug development through retrospective analysis of relevant existing adult and pediatric clinical trial data.

One example of a pediatric disease target where information gaps exist is in the field of hypertension. FDA hopes to develop an analytical database from completed pediatric pharmacokinetic (PK)/pharmacodynamic (PD) clinical trials of antihypertensive drugs. A key goal for 2006 is to begin converting existing electronic datasets from pediatric studies to a standardized format (C-DISC⁶) so that the data can be imported into a data repository that can be queried. Development of this pediatric trials database will allow systematic review of PK and PD studies from various data submissions and inform the design and conduct of future pediatric studies.

Accelerating the Availability of Artificial Pancreas Technologies

Opportunity #76

FDA is providing scientific and regulatory expertise to an initiative of the Juvenile Diabetes Research Foundation (JDRF) to accelerate the development of artificial pancreas

⁶ Clinical Data Interchange Standards Consortium's Study Data Tabulation Model.

technologies. This work includes re-evaluation of clinical research designed to assess continuous glucose sensors for new clinical outcome measures and development of outcome measures for reportable real time use of continuous glucose sensors and a closed loop artificial pancreas.