

# Task 1: Outline of Core FDA Regulatory Functions

## Executive Summary

The FDA Science Board has been asked to undertake a broad overview of how FDA regulatory activities are supported by its scientific capacities. Specifically, the Commissioner asked the Science Board to report to him with findings on where there are gaps between current scientific capacities and the science FDA needs today and will need in the future to accomplish its regulatory mission.

This review has been divided into six Tasks, several of which specify deliverables from FDA to the Science Board Subcommittee. The FDA deliverable for Task 1 (attached) is an Outline of Core FDA Regulatory Functions. This Outline is an enterprise-wide (not Center-by-Center) overview of the key regulatory activities that FDA must undertake to discharge its statutory responsibilities to protect and promote the public health, and that must be informed and supported by modern science and technology.

FDA regulatory functions divide roughly into three Core categories:

- Core Activity #1—Pre-Market Review
- Core Activity #2—Marketed Product Adverse Event Surveillance and Efficacy/Safety Assessment
- Core Activity #3—Ensuring Marketed Product Quality and Safety

In addition, the Outline describes several categories of Supporting Activities necessary for execution of our regulatory responsibilities.

The boundaries between these Core function can be porous; some regulatory functions cross boundaries. Not all Centers undertake all of these functions, and many functions apply to several Centers.

We hope this outline will serve the Subcommittee as a foundational document for this Review. In particular, we hope it will assist the Subcommittee's efforts to identify the limitations of today's regulatory science, develop future projections, and identify science needed for a modernized FDA, by providing a map for those inquiries.

## REGULATORY ACTIVITIES

### Core Activity #1—Pre-Market Review

Pre-marketing regulatory activities involve identifying or receiving sponsor applications and submissions, reviewing and assessing them, and developing and/or implementing an FDA response for new, supplemental, and change-in-use products. Applications and submissions for Pre-marketing include:

- Biologic License Applications (BLAs)
- Pre-Investigational New Drugs (Pre-INDs)
- Investigational New Drugs (INDs)
- New Drug Applications (NDAs)
- Abbreviated New Drug Applications (ANDAs)/Generics
- Over The Counter Submissions (OTCs)
- Investigational Device Exemptions (IDEs)
- Pre-Market Approvals (PMAs)
- Pre-Market Notifications (510Ks)
- Product Development Protocols (PDPs)
- Orphan Product Designations
- Orphan Grant Submissions
- Humanitarian Use Device Designations (HUDs)
- Humanitarian Device Exemptions (HDEs)
- Request For Designations (RFDs)
- Investigational New Animal Drug Exemptions (INADs)
- New Animal Drug Applications (NADAs)
- Abbreviated New Animal Drug Applications (ANADAs)
- Feed Additives
- Investigational Food Additive Petitions (IFAPs)
- Food Additive Petitions (FAPs)
- Color Additives Petitions (CAPs)
- Emergency Use Authorization Requests
- Food Contact Notifications (FCNs)
- Export Authorization Requests
- Minor Use/Minor Species (MUMS) applications
- Generally Recognized as Safe Notices (GRAS Notices)

These activities focus on information contained in applications and submissions. Responses can include: approval, approvable, complete response, non-acceptance, non-approval, objection, clearance, a not substantially equivalent decision, information/advice letter, direction for product re-submission, a product or clinical hold, and/or a refuse to file.

These regulatory activities are iterative and complex, include multiple sub-levels of activity, and require an array of scientific and analytic activities, as well as project management and communications.

1.1 Review and Assess InVitro/Bench Data (this category applies to data received during stages prior to marketing application; for similar information submitted in marketing application see Activity 1.7)

- a. Review and assess laboratory test data to determine adequacy of preclinical data to support human testing
- b. Research and analysis to develop and qualify disease or product biomarkers
- c. Develop or evaluate test methods

1.2 Review and Assess Animal and Toxicology Data (this category applies to data received during stages prior to marketing application; for similar information submitted in marketing application see Activity 1.7)

- a. Review and assess animal pharmacology and toxicology data, to determine: adequacy of preclinical safety data to support human testing; safety assessment of infant formula, food additives and contact substances, new dietary ingredients, [color additives, GRAS food ingredients]
- b. Research and analysis to develop and qualify disease or product biomarkers
- c. Develop or evaluate test methods
- d. Good Laboratory Practices site inspections

1.3 Review and Assess Data from Tests in Animal Models

- a. Review/evaluate data in IND/IDE/510k submissions to determine whether preclinical efficacy data support the proposed clinical testing plan
- b. Review of data supporting efficacy for treatments of CT agents (Animal Efficacy rule)
- c. Research and analysis to develop and qualify disease or product biomarkers
- d. Develop or evaluate test methods and animal models

1.4 Oversee Clinical Trials of Investigational Medical Products and Food Ingredients

- a. Review proposed protocols for: adequate safety, appropriate trial design and data analysis (including appropriate endpoints and safety biomarkers)
- b. IRB and clinical trial site inspections, monitoring trials to ensure patient protections (BiMo)
- c. Receive, analyze and respond to complaints

1.5 Review Manufacturing and Product Quality for Investigational Studies (this category applies to data received during stages prior to marketing application; for similar information submitted in marketing application see Activity 1.7)

- a. Product characterization review (e.g., review identity, potency, sterility, materials compatibility, prototype and materials review)
- b. Product manufacturing processes and stability review (includes drug synthesis, drug and biologic impurities assessment, quality control methods, Good Manufacturing Practices inspection)
- c. Develop or evaluate test methods

1.6 Review, Assess, and Respond to Requests for "Humanitarian" Uses of Investigational Products

1.7 Review Marketing Applications and/or Product Notifications (including re-submitted products, efficacy supplements, transgenic/genetically modified animals)

- a. Review of clinical safety and/or efficacy results (for human medical products, infant formula, food and color additive, GRAS food ingredients, feed additives, new dietary ingredients, review of food health claims)
  - i. statistical review
  - ii. clinical review (including adverse events)
  - iii. clinical pharmacology review
  - iv. pediatric assessment for development, if under Pediatric Research Equity Act
  - v. review of biologic equivalence (generics)
  - vi. literature review (e.g., Generally Recognized As Safe notifications)
- b. Review non-clinical data supporting marketing application.
  - i. human food safety (review/validate sponsor's NADA in vitro test method for drug residues in animal tissues and milk, safety review for food and color additives, review test methods)
  - ii. review of any special toxicologic studies, e.g., reproductive toxicology or carcinogenicity
  - iii. Animal Efficacy review, where applicable
  - iv. review food nutrient content claims
  - v. review of device performance
  - vi. review of chemical equivalence (generics)
  - vii. lot release: vaccines, gene therapy, blood and blood products
  - viii. literature review (e.g., Generally Recognized As Safe notifications)
- c. Review of the effect of products on the environment
- d. Review variance and exemption requests for radiation emitting products (that are not otherwise medical devices)
- e. Manufacturing Review (including supplements), Good Manufacturing Practices
  - i. review of manufacturing processes and controls, stability review (includes drug synthesis, drug and biologic impurities assessment, quality control methods)
  - ii. microbiology
  - iii. lot release testing plan development/review (including method development)
  - iv. product characterization review (includes review identity, potency, sterility, materials compatibility, prototype and materials review)
  - v. pre-license facility inspections
- f. Safety review (of information not from pre-clinical or clinical testing)
  - i. failure mode analysis, name confusion, abuse potential
  - ii. evaluation of risk management/pharmaco-vigilance plan, (risk/benefit analysis)
- g. Label review: risk and benefit communication, instructions for use
- h. Review promotional material

## 1.8 Consultative Meetings with Sponsors

## 1.9 Standards/Guidance Development

- a. Scientific Standards – development of technical and scientific standards, domestic and international harmonization of such standards (e.g., for bench and preclinical assessment; for product development such as product specific clinical trial designs, statistical standards; for product manufacturing and quality)

- b. Data Standards – development of data standards (e.g., electronic standards for submissions, ingredient terminologies, labels), domestic and international development and harmonization of such standards

## **Core Activity #2—Marketed Product Adverse Event Surveillance and Efficacy/Safety Assessment**

These regulatory activities involve identifying or receiving information about marketed product safety or efficacy issues, verifying, reviewing, and assessing that information, and developing and/or implementing an FDA response. These activities focus on information obtained from post-market safety reports from sponsors and individuals (so called “passive surveillance”), population based surveillance studies (so called “active surveillance”), phase IV studies, as well as interactions and data obtained from other domestic and international public health agencies. (Unlike the activities listed in #3, these focus on the effects of regulated products on people, animals, or the environment.) These activities can occur in both routine and emergency situations. Responses can include: inspections, follow-up and work with product sponsors, work with local public health agencies, recalls, label changes, issuance of health alerts, product recalls and withdrawals, and legal action.

These regulatory activities are iterative and complex, include multiple sub-levels of activity, often extensive investigations, science-based interactions with third parties, and require an array of analytic activities and extensive risk communications activities.

### **2.1 Receive and Analyze Reports of Adverse Events, Accidental Radiation Occurrences, Product Failures**

- a. Establish and manage procedures to receive and assess reports and complaints
- b. Establish links to external entities (e.g., other public health agencies) to monitor or evaluate reports (e.g., food contamination outbreaks, infectious disease outbreaks, tissue drug residues.)
- c. Design/undertake studies of data received (e.g., studies required by Best Pharmaceuticals for Children Act)

### **2.2 Active Surveillance / Signal Detection Activities**

- a. Surveillance and characterization of antimicrobial susceptibility patterns of food-borne bacteria from retail meats
- b. Product studies: Post-marketing study design and data review (e.g., studies required as a condition of product approval, other phase 4 studies, industry device studies required by CDRH under section 522)
- c. Population-based studies: Design/undertake population and meta-data studies (e.g., epidemiologic, sample surveys, lit searches, including use of data in marketing applications), studies on automated data bases of claims or electronic medical records for epidemiologic assessment of safety concerns.
- d. Monitoring for illegal sale of FDA-regulated products
- e. Oversight of changes made to marketed devices

- 2.3 Methods Development
  - a. Develop analytical methods for signal detection and evaluation, design and undertake studies to evaluate signals
  - b. Research and analysis to develop and qualify new safety biomarkers based on surveillance information
  - c. develop sampling and detection methods for surveillance for priority chemical, microbiological, and radiological agents in vulnerable foods
- 2.4 Take Action on Safety/Efficacy Problems
  - a. Investigations, follow up with sponsors
  - b. Review manufacturer corrective action plans, design and evaluate risk management programs
- 2.5 Implement and Evaluate Risk Communications (public announcements, safety alerts, label changes), develop risk communication materials appropriate to specific audiences, dissemination, implement actions such as label changes)
- 2.6 Emergency Response Preparation and Crisis Management
  - a. Work with domestic and international partners to prepare for and respond to public health threats and crises (e.g., pandemic, counterterrorism)
  - b. Work with the industry on procedures to address terrorism and compliance with any relevant regulations
- 2.7 Standards/Guidance Development
  - a. Scientific Standards – development of technical and scientific standards, domestic and international harmonization of such standards
  - b. Data Standards – development of data standards (e.g., electronic standards for submission of adverse event information), domestic and international development and harmonization of such standards

### **Core Activity #3—Ensuring Marketed Product Quality and Safety**

These regulatory activities involve identifying or receiving information about a marketed product, manufacturing/distribution facility, or importing facility; verifying, reviewing and assessing that information; and developing and/or implementing an FDA response. Unlike the activities in #2, these activities focus on information obtained from facilities inspections, product quality inspections, and other information about the product itself and/or the facility (versus about the product's effects on people, animals, or the environment). These activities can occur in both routine and emergency situations.

Responses can include: inspections, intensive follow-up and work with product sponsors or distributors, work with import agencies, product recalls and withdrawals, and legal action.

These regulatory activities are iterative and complex, include multiple sub-levels of activity, often extensive investigations, science-based interactions with third parties, and require an array of analytic activities and extensive risk communications activities.

- 3.1 Inspect and Evaluate Products and Manufacturing Facilities
  - a. Annual and risk-based manufacturing inspections and oversight (including distribution facilities and warehouses, federal mammography facilities), Good Warehouse Storage/Practices inspections, product sample collection and analysis
  - b. Imported products and import facilities
    - i. assess import examination data to ensure safe importation of products
    - ii. monitor imports/counterfeits and tracking
    - iii. transgenic/genetically modified animals
  - c. Implement/Oversee Quality Management Programs (cGMPs, HAACP, QSR), encourage adoption of robust quality systems (to detect, correct, and prevent product defects)
  - d. approval and oversight of accreditation bodies and inspectors for products/manufacturing facilities
  - e. Oversight of marketed products (e.g., design and evaluate risk management programs, receive and assess product deviation reports, annual reports, published literature, safety analysis of cosmetic ingredients), investigate complaints
- 3.2 Methods Development (develop test methods, forensic and other, e.g., develop/validate methods for bacterial antimicrobial susceptibility, drug residues and prohibited animal proteins in animal-derived foods and animal feeds)
- 3.3 Industry Outreach and Education
- 3.4 Implement and Evaluate Risk Communications
- 3.5 Product Shortage Activities (receive reports, investigate, medical necessity determination, potential action, consultation)
- 3.6 Review Electronic Product Radiation Safety Reports
  - a. review product conformance to applicable radiation safety performance standards
  - b. review manufacturer quality control testing program for ability to ensure product conformance and safety
- 3.7 Advertising Review and Monitoring
- 3.8 Facility and Product Registration/Listing Activities
  - a. Review facility registrations, ensure completeness, assign unique registration number.
  - b. Review product listings, review the product listing for completeness, assign the owner/operator a unique listing number.
  - c. Review export certification requests: confirm products being exported: are freely marketed in the US; are in compliance with US and importing country's requirements; meet certain national or international standards, such as quality standards; do not contain specific contaminants.

- 3.9 Standards/Guidance Development
- a. Scientific Standards – development of technical and scientific standards, domestic and international harmonization of such standards (e.g., packaging standards, food safety standards, food processing technologies, time/temperature for pasteurization, guidelines under heightened threat alerts, hospital transfusion services)
  - b. Data Standards – development of data standards (e.g., electronic standards for listing information), domestic and international development and harmonization of such standards

## SUPPORTING ACTIVITIES

### S.1 BioInformatics Activities

- a. Develop and maintain IT systems to allow sponsors to submit marketing applications to FDA electronically (including capacity to capture data from pre-market submissions and reviews and provide searchability for future reviews and guidance development)
- b. Develop and maintain IT systems to receive and process adverse event reports, product deviation/failure reports, and other safety-related report electronically from sponsors, consumers, and others.
- c. Develop and maintain IT systems that link to external systems that monitor or evaluate adverse events, or to support other data exchanges (e.g., link to CDC systems for information on food contamination outbreaks, infectious disease outbreaks, weekly transfer of certified mammography facility data to CMS, CFSAN data exchanges with USDA, data from CDC on vaccines, tissues)
- d. Develop and maintain electronic dictionaries: product names and classes; adverse event classification; product types.
- e. Develop and maintain IT systems that support product and facility listing/registration activities
- f. Develop and maintain IT systems that allow access to and processing of information from large adverse event/medical databases
- g. Develop and maintain IT systems to support risk communications to stakeholders (e.g., robust list-serves)
- h. Develop and maintain IT systems that support internal information dissemination (about FDA policies and updates, scientific issues, public health matters)
- i. Develop and maintain IT systems to manage regulatory development (tracking, capture of public comment)
- j. Develop and maintain an IT system to supports specialized scientific tools for regulatory review and research

### S.2 Enforcement (legal actions, investigations, recalls)

### S.3 Education (of manufacturers, sponsors, clinical investigators, IRBs, medical community, consumers, etc.)

### S.4 Training FDA Personnel (e.g., ongoing training in new science)

### S.5 ORA Field Resources

# Task 2: Identify Limitations of Today’s Regulatory Science, Mapped to Regulatory Functions

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## Executive Summary

The following is the second FDA deliverable to the Science Board Subcommittee, in support of its review of FDA science and research. The FDA deliverable for Task 1 was an enterprise-wide outline of core regulatory activities that FDA must undertake to discharge its statutory responsibilities to protect and promote the public health, and that must be informed and supported by modern science and technology. Here we provide the FDA deliverable for Task 2, information about current scientific limitations and major opportunities for modernizing FDA regulatory science, mapped to the core regulatory functions identified in Task 1. Specifically, the attached material identifies FDA's views of:

1. Key Scientific Limitations and Opportunities for Modernizing Regulatory Science at the FDA. The core of FDA's deliverable for Task 2 is a Center-by-Center description of the major scientific limitations that are currently impeding the ability of FDA to execute its regulatory responsibilities in the most effective way possible, and some examples of opportunities for modernization in each area. The problems identified may stem from limitations in FDA access to existing science and technology to the need for new scientific knowledge. This is not an inventory of all scientific issues we are facing; rather, these are the priority issues which present the greatest opportunity for improvement.

2. The Categories of Scientific Expertise that FDA Needs to Undertake its Current Regulatory Responsibilities. Table I, the Scientific Expertise Listing for a Modernized FDA, displays an enterprise-wide overview of the scientific disciplines needed today. For each category of expertise, Table 1 identifies which FDA Centers need experts in that field and examples of the kinds of regulatory activities for which that area of expertise is required. This Table does not indicate actual available expertise. Rather, it represents an FDA-wide view of the full range of scientific expertise that should be deployed in support of our public health mission.

3. How Current Scientific Limitations Map to Our Core Regulatory Functions. Table 2, Current Scientific Limitations Mapped to Core Regulatory Functions, is a cross walk between FDA's core regulatory activities and the scientific issues identified by the Centers in Task 2. This is an enterprise-wide overview of regulatory functions that could be most improved by enhancement of FDA's regulatory sciences, and a view of many commonalities in scientific issues across the Centers.

We hope this Task 2 deliverable will serve as one touchstone for the Subcommittee's work to identify limitations of today's regulatory science and identify the science needed for a modernized FDA.

## Center for Biologics Evaluation and Research (CBER)

### PREDICTIVE BIOMARKERS FOR BIOLOGICS MEDICAL PRODUCTS—CBER #1

#### Current State

Under current state, cell products often fail to function properly in the patients, or the cells die soon after administration in addition, undetected populations of cellular contaminants could lead to adverse outcomes such as cancer, such as immunogenicity. Despite being 21<sup>st</sup> Century Medicine, CBER has 19<sup>th</sup> and 20<sup>th</sup> Century technology to ensure the safety, efficacy and quality of cell therapy products that have the potential to cure serious diseases such as diabetes, dementia and heart disease. Technologies such as histology, karyotyping, immunohistochemical staining analyses are insufficiently sensitive and predictive of the clinical outcomes of cellular products.

#### Scientific/Technical Limitation

Need for identification of cellular product biomarkers predictive of desired clinical outcomes to predict safety and efficacy (e.g., insulin production from pancreatic islet function; tumor risk for stem cell-derived products for nervous system, heart).

#### Scientific Areas

Animal Science, Bioinformatics, Cell Biology, Developmental Sciences, Genetics, Genomics/Microarrays, Health Sciences, Molecular Biology, Neuroscience, Physiology, Toxicology Proteomics.

#### Examples of Strategic Opportunity

With the new technologies and expertise, scientific knowledge and tools to develop new FDA guidances will provide better regulatory pathways that will lead to cellular therapy products that survive better, perform better and produce desired clinical outcomes, thus leading to licensure and availability of these 21<sup>st</sup> Century medicines.

## **NEW APPROACHES TO PRE-MARKET REVIEW OF GENE THERAPY PRODUCTS— CBER #2**

### Current State

(i) Retroviral gene therapy vectors can cure fatal diseases such as inherited immune deficiencies, but also can cause fatal cancer in the patients who receive these therapies. There are no preclinical toxicology tests to predict adverse events from gene vector therapy and to identify which vector features could be modified to improve safety outcomes.

(ii) Adenoviral gene therapy is used to deliver life-saving, disease curing therapies. Low doses of vector often fail to reach the intended target cells due to inefficient vector delivery, thereby requiring high doses, which are effective but often produce serious adverse events, such as fatal respiratory distress syndrome. Currently no good preclinical tests are available to predict and resolve the efficacy problems and adverse event risks.

### Scientific/Technical Limitation

(i) Need validated new toxicology approaches and methods for gene vector therapies, whereby comparisons of vector designs can predict cancer risk of these products, including large, long term toxicology studies in animals.

(ii) Need tests to predict preclinical safety and efficacy risks, and use these methods to help sponsors identify features of vectors or delivery systems that improve efficacy and reduce adverse events in recipients.

### Scientific Areas

(i, ii) Animal Science, Bioinformatics, Cell Biology, Developmental Sciences, Genetics, Genomics/Microarrays, Health Sciences, Molecular Biology, Neuroscience, Proteomics, Physiology, Toxicology.

### Examples of Strategic Opportunity

(i) New toxicology approaches for complex biological products such as gene vectors to predict cancer risk, can be used to develop FDA guidances. Will result in new vector designs with reduced risk of cancer and more efficient licensing of these life-saving therapies.

(ii) Developing the scientific knowledge and tools to develop FDA guidance will support adenovirus vector gene therapy products' successful delivery of therapeutic genes with lower doses of vector and fewer adverse events.

## **EVALUATION METHODS FOR TISSUE PRODUCT QUALITY AND SAFETY—CBER #3**

### Current State

Human tissue products have been associated with infectious agent transfer to recipients. Currently these products are tested for microbial contamination by standard microbiology methods that provide delayed results and are insensitive for testing of tissues due to inadequate sampling paradigms.

### Scientific/Technical Limitation

Need to develop new methods for rapid, sensitive testing for microbial contamination using samples representative of the tissue in order to better ensure product safety.

### Scientific Areas

Animal Science, Bioinformatics, Cell Biology, Developmental Sciences, Genetics, Genomics/Microarrays, Health Sciences, Molecular Biology, Neuroscience, Physiology, Proteomics, Toxicology.

### Examples of Strategic Opportunity

Developing the scientific tools and knowledge to create FDA guidance on new testing methods will increase the availability of safer tissue products causing fewer infections in recipients.

**PRE-MARKET REVIEW OF VACCINE THERAPIES—CBER #4**Current State

Tumor vaccines and immunotherapies hold tremendous promise as a new type of cancer therapy. A large number of tumor vaccines and immunotherapies are in clinical trials, but we do not have the scientific information to develop valid methods for product characterization and for potency tests that will be predictive of safety and efficacy outcomes.

Scientific/Technical Limitation

Need new product biomarkers with correlative studies of successful induction of immune responses in animal models and patients, linked to efficacy in clinical trials.

Scientific Areas

Animal Science, Cell Biology, Developmental Sciences, Genetics, Genomics/Microarrays, Health Sciences, Immunology, Molecular Biology, Neuroscience, Proteomics, Bioinformatics, Physiology, Toxicology.

Examples of Strategic Opportunity

Development of scientific knowledge and methods to create FDA guidance on choice of better predictors of safety, efficacy and potency of tumor vaccines and immunotherapies will facilitate advanced development to approval and a new approach to curing and monitoring cancer.

## **RISK MANAGEMENT IN EVALUATING NOVEL APPROACHES FOR TISSUE ENGINEERING—CBER #5**

### Current State

(i) Human organs for transplantation in short supply, so many people die while awaiting transplants. Natural or transgenic animals can be a source of organ transplants (e.g., xenotransplantation) but xenotransplantation product efficacy and safety is limited by immune rejection by the recipient. Lacks of understanding of the reasons for rejection, and lack of tests to predict and avoid or reduce rejection risk, have blocked development of this potentially life-saving approach.

(ii) Human organs for transplantation are in short supply so many people die while on awaiting transplants. Under development is tissue engineering, a source of organs and tissues grown from cells on artificial scaffolding (e.g., artificial bladders, artificial pancreas). Moreover, if organs and tissues are engineered from the patient's own cells, tissue/organ rejection, a major problem associated with standard allogeneic transplants may be reduced or avoided. However, as a new and emerging technology, CBER lacks the regulatory pathways and testing methods for tissue engineered products and answers to the key questions for evaluating safe and effective products.

### Scientific/Technical Limitation

(i) Need to develop approaches to suppress, evade, bypass, or reduce immunity to xenografts, without the use of immunosuppression so potent that infections result and cause additional adverse events. With new measures in place, we will need tests to predict risk for rejection of xenotransplanted products.

(ii) Need to develop the scientific tools and knowledge to evaluate organs and tissues produced through tissue engineering.

### Scientific Areas

(i) Animal Science, Bioinformatics, Cell Biology, Developmental Sciences, Genetics, Genomics/Microarrays, Health Sciences, Immunology, Molecular Biology, Neuroscience, Physiology, Proteomics, Toxicology.

(ii) Animal Science, Bioinformatics, Cell Biology, Developmental Sciences, Engineering, Nanobiology, Genetics, Genomics/Microarrays, Health Sciences, Immunology, Molecular Biology, Neuroscience, Physiology, Proteomics, Toxicology.

Examples of Strategic Opportunity

(i) Development of the scientific knowledge and tools to create FDA guidance will permit approval of xenotransplantation technologies, leading to more plentiful supply of organs and tissues for transplantation to treat diseases and save lives.

(ii) Development of the scientific knowledge to create FDA guidance and development of methods for evaluating the safety and efficacy of engineered tissues and organs will facilitate efficient development of new regulatory pathways and open a major, new area for treatment of serious illnesses such as renal, cardiac and hepatic disease. Developing an inter-Center Tissue Engineering Working Group will facilitate efficient evaluation and approval of these products.

## PRE-MARKET GUIDANCE AND REFERENCE STANDARDS FOR BLOOD PRODUCTS—CBER #6

### Current State

- (i) Blood and blood products may be contaminated with infectious, transmissible organisms, including emerging infections diseases (e.g., Pandemic influenza, West Nile Virus, WNV; Transmissible Spongiform Encephalopathies, TSE) and agents of bioterror (e.g., anthrax). Current Guidances for blood donor tests and product quality tests and current reference standards and reagents for these tests are available only for a limited number of organisms of concern for blood and blood product safety. Current blood donor tests may not detect new genetic variants of some important blood-borne infections, e.g., HIV and WNV.
- (ii) Plasma derived products may stimulate an undesired immune response to the product that may limit product efficacy and increase adverse events due to allergic-type reactions (“neoantigenicity”). Standard animal based testing methods are not reliable for predicting the individual recipient’s risk of immunogenicity and neoantigenicity of plasma-derived and recombinant products.
- (iii) Historically, antibody treatments (“passive immunization”) are among the fastest and most effective ways of treating catastrophic, epidemic infections when timing does not permit the weeks required for vaccination to generate an active immune response. However, there are many infectious diseases for which no clinical studies are available to document the efficacy of passive immunization and for which no animal models are available to predict efficacy of immune globulin product treatment or prophylaxis, e.g., for many emerging and bio-defense-related pathogens under the Animal Efficacy Rule. Further, concerns are raised in that some emerging infections such as SARS may become worse as a result of antibody enhancement of disease.

### Scientific/Technical Limitation

- (i) Need (a) development of new methods and reference standards for blood donor and blood product testing for bioterror agents and emerging pathogens to improve consistency and quality of blood and blood products, (b) need to upgrade current detection technologies to support improved sensitivity and speed (e.g., multiplex platforms) for pathogen detection, by rapidly testing donors for several pathogens at one time using relatively small sample volumes and c) Need to continually evaluate licensed blood donor tests for their ability to detect new genetic variants of blood borne infectious diseases.
- (ii) Need to (a) replace costly and time consuming animal based tests with in vitro techniques/tools/pharmacogenomics for accurately detecting the subtle changes to recombinant and plasma-derived products that lead to enhanced, undesirable immune responses to these products that result from necessary manufacturing procedures, (b) bridging animal studies to qualify the in vitro testing methods, and (c) genomics studies to identify patients at high risk for these undesired outcomes.

- (iii) Need appropriate animal models and clinical trials for testing efficacy and safety of immune globulin products used for emerging infectious diseases and bioterrorism agents to protect the nation's health.

#### Scientific Areas

- (i) Animal Science, Bioinformatics, Cell Biology, Genetics, Genomics/Microarrays, Health Sciences, Molecular Biology, Proteomics.
- (ii) Bioinformatics, Chemistry, Clinical Trial Design, Genetics, Genomics, Health Sciences, Immunology, Mathematics/Statistics, Microbiology.
- (iii) Animal Science, Clinical Trial Design, Genomics, Health Sciences, Immunology, Microbiology, Mathematics/Statistics, Proteomics.

#### Examples of Strategic Opportunity

- (i) Development of scientific knowledge and tools to create FDA guidance to a) facilitate evaluation of blood donor and blood product tests for emerging and bioterror pathogens such as malaria, Pandemic influenza, HHV8, Chagas, Malaria, Babesia, Leishmania, (b) upgrade existing diagnostic technologies to improve speed, and reduce testing costs and product loss in blood donor testing and (c) evaluate licensed blood donor tests for ability to detect genetic variants of HIV, WNV and other blood-borne infections.
- (ii) Developing the scientific knowledge and tools to create FDA Guidances and new pharmacogenomic-based personalized medicine will enhance product success, reduce testing times and costs, and facilitate new product development. For example, new in-vitro methods to detect subtle changes in molecules will improve product success by identifying successful product candidates early in the development process. Mass spectrometry, proteomics, phage display libraries can be used to identify new non-linear epitopes likely to lead to increased risk of neoantigenicity. Bridging in vitro studies with animal based methods and clinical trial outcomes will reduce the need for clinical trials and human subject sizes leading to faster development times at reduced costs.
- (iii) Developing the scientific knowledge and tools to create FDA Guidance on clinical trials and/or animal models applicable to the Animal Efficacy Rule for emerging and biodefense related immune globulin products (e.g., smallpox, anthrax, ebola, pandemic influenza) would facilitate national preparation for response to these agents.

## **PRE-MARKET GUIDANCE AND REFERENCE STANDARDS FOR BLOOD PRODUCTS—CBER #7**

### Current State

Standard General Toxicity evaluation protocols and animal models (“one-size-fits-all” approach) were established for blood products a long time ago, when products were simpler and technologies were limited. Currently, complex blood products safety and efficacy are of increasing concern as these preclinical tests may be inadequate, thus putting clinical trial subjects at risk and causing expensive product failures late in product development.

### Scientific/Technical Limitation

Need better, more predictive pre-clinical test such as in vitro cell culture and small animal models for toxicity evaluation of blood products to improve predictability of pre-clinical testing for efficacy and safety of blood products.

### Scientific Areas

Animal Science, Biochemistry, Cell Biology, Health Sciences, Molecular Biology, Organic Chemistry.

### Examples of Strategic Opportunity

FDA Guidances based on improved technologies will equip FDA with better product evaluation tools and facilitate new blood products to market, e.g., use of pre-clinical endothelial cell cultures and small animal models predictive of toxicity of hemoglobin based oxygen carrier (“blood substitute”) and related products.

## SAFETY APPROACHES AND SURVEILLANCE METHODS FOR BLOOD PRODUCTS— CBER #8

### Current State

- (i) Nucleic acid and antigen-antibody-based pathogen detection for blood donor testing is currently in use for blood safety. However, once identified as contaminated, blood products are discarded because there are no pathogen reduction strategies for blood, blood components and related products. This threatens the blood supply in case of a bioterror attack or an epidemic of blood-borne infectious diseases.
- (ii) Some life saving blood products, such as platelets and red blood cells, may be in short supply because of limited stability and shelf life. In addition, development of storage-extension strategies is hindered by the current tests for platelet quality following extended storage, e.g., Extent of Shape Changes (ESC) and human testing of platelet recovery following radio-labeling. Using these tests, there is considerable variability in the recovery and survival of platelet products among normal volunteers and among different laboratories performing these tests, making reasonable determination of the outcome of platelet storage extension strategies difficult to determine.
- (iii) Currently not available or not available in sufficient quantities are reference standards for several pathogens and infectious agents including TSE used for testing blood donors and human and animal cell and tissue products.

### Scientific/Technical Limitation

- (i) Need development and adaptation of available pathogen reduction methods from other fields into blood product arena in order to make blood and blood products, especially platelets, RBC and immune globulins. Further, this advance needs to be supported by methods such as product quality biomarkers to ensure that the treated blood products remain safe and effective.
- (ii) (a) Need to move human testing to qualified small animal models for testing of the function and survival of platelets and red blood cells. (b) Need platelet and red blood cell biomarkers predictive of quality of stored platelets and red blood cells. (c) Bridging studies (between 'a' and 'b') to validate the predictability of the biomarkers as indicators of clinical outcomes.
- (iii) Need development of reference standards, including lot release panels for standardization and quality & safety monitoring of blood-derived products and tests kits to screen blood donors for bacteria, viruses, prions, parasites and emerging pathogens.

### Scientific Areas

- (i) Animal Science, Bioinformatics, Cell Biology, Developmental Sciences, Genetics, Genomics/Microarrays, Health Sciences, Molecular Biology, Neuroscience, Proteomics, Physiology, Toxicology.
- (ii) Animal Science, Cell Biology, Clinical Trial Design, Genomics, Health Sciences, Mathematics/Statistics, Molecular Biology, Proteomics.
- (iii) Cell Biology, Clinical Trial Design, Genomics, Health Sciences, Microbiology, Molecular Biology, Proteomics, Mathematics/Statistics.

### Examples of Strategic Opportunity

- (i) Development of scientific knowledge and tools to create FDA guidance on appropriate parameters for pathogen reduction strategies in blood products, and blood product biomarkers predictive of safety and efficacy will ensure that blood, blood components and related products are safe and in plentiful supply, particularly in the case of a national emergency such as bioterror attack or epidemic of blood-borne infectious diseases.
- (ii) Development of the scientific knowledge and tools to create FDA guidance on the development of a) small animal models and b) new product biomarkers of quality and performance to replace costly and unpredictable tests of product survivability, thereby reducing development costs, improving predictability of clinical outcomes and enhancing the quality and availability of the nation's blood supply. Further, development costs and success rates will be improved by the use of these tools in bridging studies, thereby reducing the need and costs of clinical trials for blood products.
- (iii) Availability of these materials will enhance blood product quality and safety and improve efficiency of product development and evaluation.

## **PRE-MARKET REVIEW AND PRODUCT QUALITY TESTING OF VACCINE THERAPIES—CBER #9**

### Current State

Current assays and tests available to evaluate the safety of candidate vaccines utilize older technologies, including: a) animal toxicology studies (e.g., non-human primate) to evaluate attenuation of vaccines, b) tests for the oncogenicity risk of cells used to manufacture viral vaccines and c) methods for detecting contamination of vaccine products. These tests may not be validated using 21<sup>st</sup> Century standards and are relatively insensitive, labor intensive and poorly predictive of clinical outcomes. Therefore, it is difficult to assess the safety risk and efficacy potential of many vaccines developed using advanced technologies.

### Scientific/Technical Limitation

Need new advances in preclinical and product quality testing methods for a) new vaccine products such as vectored or DNA-based vaccines, b) new immunization strategies such as novel adjuvants and c) unique delivery systems such as the transdermal delivery patch.

### Scientific Areas

Animal Science, Genetics, Genomics, Health Sciences, Microbiology, Nanotechnology, Nanobiotechnology, Proteomics.

### Examples of Strategic Opportunity

Developing the new scientific knowledge and tools to create FDA Guidance for faster, more quantitative and predictive ways to evaluate: a) cell substrates used to manufacture viral vaccines for the presence of contaminating adventitious agents and risk for oncogenicity; b) toxicology studies to measure the attenuation of live vaccines such as enteric bacteria, childhood viruses and TB; c) safety concerns for novel vaccines or vaccine delivery systems such as adenovectored vaccines and DNA vaccines; d) neurotoxicity of live viral vaccines; e) immunopathogenic risk of giving TB vaccines to previously infected subjects; f) safety issues surrounding the new technologies being developed for yearly and pandemic influenza vaccines and other vaccines for emerging diseases; g) new technologies being proposed for novel adjuvants; and h) safety of new immunization strategies such as transdermal delivery and plant vaccines, novel prime-boost strategies, and new combination vaccines will result in improvements in the safety and efficacy of vaccines, protect the public health and improve the efficiency and success of these products entering the marketplace.

## DEVELOPMENT OF PREDICTIVE BIOMARKERS AND ANIMAL MODELS FOR VACCINE THERAPIES—CBER #10

### Current State

Current biomarkers of vaccine efficacy are unsatisfactory, e.g., often relying on older technology (e.g., serology), do not exist (e.g., rotavirus) or exist but are clinically unvalidated (e.g., mumps). Further, when the efficacy of many vaccines cannot be studied in humans, e.g., anthrax, smallpox, ebola, the “Animal Efficacy Rule” permits flexibility, but many of these infections need validated animal models.

### Scientific/Technical Limitation

Need identification of correlates of immunity to serve as biomarkers for vaccines that can be used as valid efficacy surrogates in clinical trials and in animal models. Development of new animal challenge models is needed for many infectious diseases to identify and evaluate these correlates of efficacy, particularly for use with Animal Efficacy Rule. For example, need animal models for vaccines against enteric bacteria, pertussis, anthrax, TB, smallpox, and tularemia to combine with the development of in vitro assays and challenge models to identify correlates of immunity with disease. Improved clinical trial assays are needed to facilitate product development and evaluate new products in clinical trials.

### Scientific Areas

Animal Science, Genomics, Health Sciences, Immunology, Microbiology, Nanobiotechnology, Nanotechnology, Proteomics.

### Examples of Strategic Opportunity

Development of new scientific knowledge and tools to create FDA guidance on application of the “Animal Rule” for those vaccines that cannot be evaluated in human clinical trials for efficacy. Data provided by animal models of efficacy will enhance the efficiency and success of licensure of new and improved vaccines, including anthrax, annual and Pandemic Influenza, ebola, smallpox, tularemia, rotavirus and other childhood diseases, HIV, TB, etc. Development of predictive and validated biomarkers, e.g., immunoassays and diagnostics for clinical trials will improve predictability of outcomes and reduce costs of these studies.

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## STATISTICAL APPROACHES FOR BIOLOGICS CLINICAL DATA SETS—CBER #11

### Current State

Currently there are limited numbers of statistical approaches for analyzing submitted data.

### Scientific/Technical Limitation

- Need better statistical methods for analyzing small set and sparse data, statistical analysis of potency evaluation in bioassay
- Need statistical methods for analyzing and modeling animal and toxicity data in experimental settings and their projections into human responses.
- Need to apply Bayesian procedures and meta-analysis approaches to clinical data, as well as statistical methods of signal detection and data mining.
- Need to apply methodologies of mathematical modeling and clinical trial simulation (in silico biology) to examine the effects of the PK/PD response of biological product, variability of individual patients, and trial design parameters on the safety and efficacy outcomes.
- Need to apply the methodologies of statistical genetics to evaluate genetic associations (candidate gene and genome-wide studies) with safety and efficacy measurements in clinical trials.

### Scientific Areas

Bioinformatics, Clinical Trial Design, Computing Science, Genomics, Health Science, Mathematics/Statistics, Proteomics.

### Examples of Strategic Opportunity

New scientific knowledge and tools create FDA guidance and using these new statistical tools will provide for more accurate data analysis and better support of the availability of safe, effective and high-quality biological products. Bayesian procedures and meta-analysis approaches would support proper pooling of data from various studies and sources and would increase the power of detecting signals of safety and efficacy.

## DIAGNOSTIC TESTING OF BIOLOGICS MEDICAL PRODUCTS—CBER #12

### Current State

Currently, successes or failures of vaccines in clinical trials are often based on “soft” clinical criteria of breakthrough infection without specific, established and agreed upon guidelines of disease diagnosis, e.g., serological tests that do not distinguish between HIV and TB vaccination and infection; serological vs. culture diagnosis of whooping cough; identification of sub-clinical cases of mumps infection. Further, disease threats such as malaria, dengue and TB that exist predominantly in developing countries pose an important global public health concern. Yet, many diagnostic tests for global diseases are too cumbersome and expensive for use in developing countries.

### Scientific/Technical Limitation

Need validated methods for disease diagnosis that can be used in clinical trials in developed and developing countries. Need to work with global partners, including international regulatory authorities and other US agencies to facilitate the development of validated biomarkers of disease to support new products to combat continuing and emerging global public health threats in domestic and international settings.

### Scientific Areas

Epidemiology, Genomics, Health Science, Immunology, Mathematics/Statistics, Nanobiotechnology, Nanotechnology, Microbiology, Proteomics.

### Examples of Strategic Opportunity

Development of new scientific knowledge and tools will create FDA guidance for diseases such as AIDS, whooping cough, meningococcal disease, smallpox, malaria, TB, rotavirus and other childhood diseases and for allergenics for diagnostics and immunotherapy to advance the clinical study and development of new vaccines and related products to inhibit domestic and worldwide health threats.

## PRODUCT QUALITY & SAFETY STANDARDS FOR BIOLOGICS MEDICAL PRODUCTS—CBER #13

### Current State

- (i) Complex biological products are large, variable and the active components of the products are often undefined. Current methods for characterizing complex biological products may be cumbersome, crude, nonspecific and use decades-old technologies. These methods are typically insufficient for accurate comparisons between products and even to detect some lot-to-lot variations of the same product. Concerns for consistency, safety and other quality issues result. Further, many complex biological products lack well characterized reference standards to facilitate licensed product consistency and new product development.
- (ii) Currently the majority of complex biological products regulated by CBER are released to the marketplace through the formal “Lot Release” process. Many of the novel or critical products undergo testing in CBER laboratories. Quality testing needs to advance to keep ahead of increasing ISO and other quality standards being applied.

### Scientific/Technical Limitation

- (i) Need development of better and more accurate product quality characterization methods using new technologies to provide accurate and clinically relevant information about product quality and consistency, and to develop reference standards for distribution to sponsors and product developers.
- (ii) Need to expand and develop the capacity for quality systems in product testing laboratories at CBER.

### Scientific Areas

- (i) Cell Biology, Genomics, Microbiology, Manufacturing Science, Molecular Biology, Proteomics.
- (ii) Cell Biology, Chemistry, Genomics, Immunology, Microbiology, Mathematics/Statistics, Proteomics.

### Examples of Strategic Opportunity

- (i) Development of new scientific knowledge and tools creates FDA guidances and providing new method and reference standard development will improve the clinically relevant characterization of complex biological products, identification of active components of these products, support more efficient evaluation of product quality and consistency and supply needed reference standards for licensed and candidate products such as TB vaccine, annual and Pandemic Influenza vaccine, rabies vaccine, acellular pertussis and other childhood vaccines.

- (ii) A quality laboratory initiative developed in CBER will provide improved Lot Release testing of the complex and difficult to characterize vaccines, such as annual and Pandemic Influenza vaccine, and blood/blood products, thereby improving product quality.

**POST-MARKET SURVEILLANCE OF BLOOD PRODUCTS—CBER #14**Current State

Blood adverse event reporting beyond death reports is needed to fully appreciate and respond to blood product safety concerns.

Scientific/Technical Limitation

Need multidisciplinary CBER Blood Safety Team to advance blood adverse event monitoring, including to track non-fatal serious AE's in addition to death reporting.

Scientific Areas

Chemistry, Epidemiology, Health Sciences, Pharmacology, Mathematics/Statistics, Physiology.

Examples of Strategic Opportunity

A multidisciplinary "CBER Blood Safety Team" and tracking of improved blood and blood product specific population based data will clarify risks and develop preventative medical interventions to improve blood safety.

## POST-MARKET SURVEILLANCE AND QUALITY ASSURANCE OF BIOLOGIC MEDICAL PRODUCTS—CBER #15

### Current State

- (i) Passive surveillance of human cells, tissues and cellular and tissue-based product adverse reactions under current reporting requirements does not provide the data necessary to determine actual rates of such reactions. It is also difficult to determine whether or not surgical site infections are allograft associated. Further, once adverse events are reported, it is difficult to track transplants to the recipients to provide active follow-up of known events.
- (ii) Currently lack standardized adverse event definitions in vaccine safety, impeding comparisons of clinical trial data with observational and surveillance data after licensure.
- (iii) Primary reliance on manual review of individual adverse events reports limits ability to detect significant trends, leading to missed opportunities to identify developing safety concerns.
- (iv) Vaccine safety requirements are high and small rates of serious adverse events can lead to vaccine product failures late in development or even during the post-market phase. Virtual inability to predict individuals at high risk for adverse events after vaccination and other biological product exposures. No biomarkers available for vaccine safety outcomes.
- (v) Paper-based reporting of vaccine and other biological product lot distribution data leads to increased data entry costs and data entry errors; thus, utilization of paper-based data for surveillance of biological product lot safety is sub-optimal.
- (vi) Reliance on passive surveillance from voluntarily submitted adverse events reports (VAERS, AERS) to monitor safety of licensed products leads to underreporting of adverse events and difficulty in detecting signals above background rates.

### Scientific/Technical Limitation

- (i) Develop population-based data on allograft implants and expected rates of allograft-associated infections. Develop better process to distinguish allograft-associated infections from nosocomial infections. Develop tracking system to allow better active follow-up of identified adverse events.
- (ii) Need cooperation and coordination of leveraged safety surveillance activities to produce higher quality data.
- (iii) Need improved analytical tools for rapid recognition of unexpected associations between regulated products and adverse events.

- (iv) Acquisition of sufficient numbers of biological specimens from patients with and without adverse events. Need capacity for identifying genetic biomarkers of safety for vaccination.
- (v) Need electronic transmission and storage of lot distribution data.
- (vi) Need access to large population-based data sets for post-marketing epidemiologic risk assessments.

#### Scientific Areas

- (i) Cell Biology, Computing Science, Epidemiology, Health Sciences, Mathematics/Statistics, Microbiology.
- (ii, iii) Bioinformatics, Computing Sciences, Epidemiology, Health Sciences, Mathematics/Statistics, Pharmacology.
- (iv, v) Computing Science, Genetics, Genomics, Health Sciences, Mathematics/Statistics, Molecular Biology, Pharmacology, Proteomics.
- (vi) Bioinformatics, Computing Sciences, Epidemiology, Health Sciences, Mathematics/Statistics, Pharmacology.

#### Examples of Strategic Opportunity

- (i) Developing the scientific tools and knowledge to create FDA guidance, a) expanding current MedSun pilot to all MedSun participating facilities, acquiring denominator data from states with active tissue programs (e.g., New York), b) continuing to work with the CDC on Transplant Transmission Sentinel Network to obtain data on allograft-associated infections and infection patterns, c) develop tracking options to allow active follow-up of recipients of transplants in the setting of known adverse events, and d) formation of the multi-disciplinary CBER Tissue Safety Team will advance the safety of these products and support these important therapies.
- (ii) FDA guidance stemming from CBER-leveraged partners, such as the Brighton Collaboration, will allow more accurate assessment of adverse event data, leading to improved public health decision making in the vaccine policy arena and improved safety of vaccines.
- (iii) FDA guidance and support arising from CBER-leveraged scientific resources with CDC, industry, academia and WHO UMC will allow development of novel techniques, software tools and systems to detect otherwise occult product risks and thereby increase biological product safety
- (iv) Development of new scientific knowledge and tools creates FDA guidance for personalized medicine approaches using specific biomarkers of vaccine safety, leading to improved safety of these and other products and greater efficiency of new product development. Examples of opportunities include employing VAERS as a source for obtaining follow-up specimens from vaccines with and without

adverse outcomes and leveraging CBER scientific resources with the CDC Clinical Immunization Safety Assessment Centers and NIH Genomics Program to develop predictive biomarkers of vaccine safety.

- (v) Electronic transmission and storage of these data will facilitate more effective utilization of these data to rapidly and accurately monitor biological product lot safety, leading to improved safety for the public health.
- (vi) Strategic opportunity to develop the multidisciplinary “CBER Vaccine Safety Team” and coordinate in developing the “Sentinel System”, and leveraging with other partners such as CMS, VA, CDC Vaccine Safety Datalink, UD General Practitioners Research Database to provide useful resources of data for key hypothesis refinements and testing by FDA. This will allow better assessment of product safety and risk management, making safety for public health better served.

**STATISTICAL APPROACHES TO BIOLOGIC PRODUCT QUALITY AND SAFETY—  
CBER #16**Current State

Currently there are limited numbers of statistical approaches for analyzing these data.

Scientific/Technical Limitation

Need better statistical process controls, and better statistical basis for product specifications and for lot release criteria.

Scientific Areas

Animal Science, Bioinformatics, Computer Science, Mathematics/Statistics, Molecular Biology, Physiology.

Examples of Strategic Opportunity

New scientific knowledge and tools create FDA guidance provided and FDA analysis using these statistical approaches will provide for more accurate data analysis and better support of the availability of safe, effective and high-quality biological products.

## Center for Devices and Radiological Health (CDRH)

### SAFETY OF MEDICAL PRODUCTS CONTAINING SOFTWARE—CDRH #1

#### Current State

Software is an integral part of a significant number of devices, and issues related to software quality and performance are increasing at a rapid pace. Due to scarcity of software expertise, often, products containing software are inconsistently evaluated by staff without expertise in the scientific area. Post-market problems related to software have been observed, and the Center needs experts to review and evaluate the proposed corrective actions.

#### Scientific/Technical Limitation

Forensic investigation related to medical device software is a new competency for CDRH. Although CDRH has developed guidances (e.g., the Content of Pre-Market Submissions for Software Contained in Medical Devices; General Principles of Software Validation) it remains challenging for staff to evaluate whether/how a product will perform its intended function. The guidance is not always followed by industry and staff without software engineering expertise cannot always determine whether software has been developed correctly.

#### Scientific Areas

Engineering Sciences (Software Engineering, Software Forensics, Software Quality Engineering, Systems Engineering).

#### Examples of Strategic Opportunity

- “Formal methods” is the term used in the software development community to describe mathematically rigorous analysis techniques used to prove assertions of reliability, safety and repeatability. The field of formal methods encompasses software forensics. Enhance FDA capabilities to diagnose software related medical device failures.
- The use of Safety Cases has the potential to enhance public safety and speed review cycles by allowing flawed assertions and incomplete evidence to be exposed.
- Standards and guidances on safety assurance and forensic analysis of medical device software would improve the speed of product development and the accuracy of product review.

## REUSE OF SINGLE USE DEVICES (SUDS)—CDRH #2

### Current State

As hospitals and healthcare facilities seek to reduce the cost of medical procedures, devices originally made for single-use, are now being reprocessed and reused many times on different patients. Manufacturers of listed reprocessed SUDs are required to submit cleaning, sterilization, and functional performance validation data in order to demonstrate that reprocessed devices remain substantially equivalent to the relevant predicate devices. Cleaning, sterilization, and functional performance validation of reprocessed SUDs include aspects of both design validation and process validation. Design validation, in this case, should incorporate both the design of the product and the design of the processes to be used in reprocessing the device.

### Scientific/Technical Limitation

While CDRH is well equipped to review traditional terminal sterilization and traditional cleaning methods, important challenges in this area include:

- validation methods to ensure that the device is clean
- the science of non-traditional sterilization methods
- standards and guidances on sterilization methods

### Scientific Area

Microbiology, Engineering Sciences (Analytical Chemistry, Chemical Engineering, Quality Engineering, Systems Engineering).

### Examples of Strategic Opportunity

- An FDA survey found that more than 45% of all hospitals with more than 250 beds reuse SUDs ranging from compression device sleeves to endoscopic/laparoscopic instruments and electrophysiology catheters. Thus, improvements in CDRH science in these areas will have wide-spread care delivery and public health benefits.

## **FAILURE ANALYSIS (DEVICE MATERIALS)—CDRH #3**

### Current State

While materials are the basic building blocks of medical devices, complex systems are getting embedded into devices. In addition, the complexity of materials and systems used in devices is increasing while test methodology and mechanistic understanding of the failure is evolving much slowly. Today, sufficient rigor may not be applied in the root-cause analysis of failure of systems, including software, electronics, materials, and devices. Hence, corrective actions may not be based on the best underlying science and engineering.

### Scientific/Technical Limitations

- Lack of test methodology and standards applicable to devices
- Lack of knowledge related to mechanistic understanding of materials failure in device-application environment
- Information sharing among pre- and post-market components of the knowledge of root-cause analysis of failure due to lack of scientific capabilities.

### Scientific Area

Engineering Sciences (Biomedical Engineering, System Engineering), Materials Science.

### Examples of Strategic Opportunity

- Medical device materials, software, electronics and mechanical systems would perform the intended function safely and effectively.
- Development and use of standards would provide confidence in the application of failure analysis methods and metrics.
- Development of guidances to clearly interpret regulations and communicate FDA thinking would aid manufacturers in understanding the regulatory requirements.

## INNOVATIVE CLINICAL TRIAL DESIGN—CDRH #4

### Current State

Clinical trials are expensive, can be inefficient, and often do not produce clear and reliable information about the safety and efficacy of a product. While market life of many device models is quite limited; yet standard clinical trials for implanted devices require long term follow-up to assess safety and effectiveness.

From a statistical point of view microarrays can create an enormous multiplicity problem, namely by chance alone without some adjustment 250 or more of the spots could appear to be statistically significant. Prediction models using microarray data have not appeared to add much if anything to the best predictive models using clinical variables only.

### Scientific/Technical Limitation

A number of approaches such as animal testing, and mathematical modeling are potential complimentary or alternative methods. However, in the interim period, improvements in the clinical trial designs offer the best approach. For this to happen, among many hurdles, active research needs to be encouraged in the development of biomarkers, imaging, innovative trial design, including:

- Design and Analysis of Medical Device Trials Using Bayesian Statistics
- Non-randomized Studies
- Active Controlled Trials
- Adaptive Trials
- Clinical Trial Simulation
- Designs for Diagnostic Products
- Drug-Diagnostic Designs

Some current software does not accommodate the large number of inputs that a microarray would have. Better predictive models are needed.

### Scientific Area

Bioinformatics, Health Sciences (Clinicians), Life Sciences (Multidisciplinary Scientists), Regulatory Statistical Science, Statistics.

### Examples of Strategic Opportunity

- New biomarkers will help move “personalized medicine” from promise to reality. These include new biomarkers to detect endpoints, use of imaging techniques for detecting end points, and assessment of risks to patients from imaging.

- Bayesian statistical methods for design and analysis of medical device trials could help us obtain more information about an experimental product that we can today.
- Better predictive models and better software would help to realize in medical product clinical trials the promise of microarrays.

**MODELING BIOLOGICAL PROCESSES—CDRH #5**Current State

Mathematical modeling is not as well advanced in biological sciences as in physical sciences.

Scientific/Technical Limitation

There is significant lack of science to utilize robust biological models of physiology and clinical understanding to reduce the size of or eliminate clinical trials. As a result, mathematical modeling is not employed as a part or full replacement of clinical trials to replace or minimize the extent of animal and clinical studies.

Scientific Area

Mathematical Modeling, Physiology, Toxicology.

Examples of Strategic Opportunity

Availability of robust, validated models of relevant biological process would allow significant improvement in trial designs, including: decrease in necessary size of trials, designs that are less burdensome on patients, use of new screening variables to optimize trial design.

Such models could also help us optimize preclinical toxicology studies to be more predictive and reduce the numbers of animals used.

## **RISK COMMUNICATION—CDRH #6**

### Current State

Today, methods for getting risk messages to the public often do not meet the needs of the intended audience. We lack tested approaches to guide communication of matters such as:

- Description of intended use/intended purpose and identification of characteristics related to the safety of the medical device
- Identification of potential hazards
- Estimation of the risks for each hazard
- The risk-benefit ratio and its public health significance

### Scientific/Technical Limitation

Today, we lack a rigorous risk communications research base and framework of principles and approaches for the communications of health risk information to diverse audiences, and a thorough understanding of the needs of the community.

In addition, we often lack the human and equipment resources to support robust electronic dissemination of public health and risk messages, web interfaces, and online databases.

### Scientific Area

Risk Analysis, Risk Communication.

### Examples of Strategic Opportunity

Improved risk communication science and resources would enable us to communicate public health information in the most optimal matter for different audiences; potential public health benefits include safer and more appropriate use of devices of all types.

Such science would support standards and guidance development to improve labeling a post-market obligations (e.g., communications related to recalls) for sponsors, and training of FDA personnel and others (e.g., training of clinicians in use of devices) related to risk communication.

## DEVICE APPLICATIONS OF GENOMICS—CDRH #7

### Current State

Genomics, including genetic testing, is flooding the regulatory space, in both drug and diagnostic development. Sponsors and other stakeholders need information and FDA input regarding both diagnostic devices and drug-related applications, including:

- development of valid biomarkers for examining drug safety and efficacy through prediction of therapeutic effect, selection of appropriate dose, and identification of risk for toxicity.
- development and review of diagnostic devices, including instrumentation and software, for identification of drug-relevant genotypes, predictive/prognostic claims, identification of pathogens singly and in panels
- specific clinical trial design strategies for trials using –omics, especially regarding use of data from technologies that yield massive amounts of data simultaneously for a given specimen
- statistical modeling of complex genomic data
- development of method and materials standards applicable to genomics
- access to regulatory requirements for genomics applications

Sponsors who are new to the regulatory arena are frequently not aware of, and have not implemented, controlled manufacturing practices, which could lead to delays in market approval/entry and significant post-market failures.

### Scientific/Technical Limitation

- Rapid evolution of product-specific technologies and statistical models requiring significant time investment in order to “keep up”
- General lack of production standards, resulting in unknown consistency of production over time for reagents and arrays; lack of regulatory science relevant to quality system regulations or GMPs for this product line
- Lack of adequate infrastructure (database capabilities, up-to-date data analysis applications, etc) to enable rapid analysis of incoming data
- Insufficient staffing to adequately address the volume and pace of innovation and data exchange
- Lack of bioinformatics expertise
- Paucity of standard quality control materials and methods for genomics applications
- Insufficient interpretive guidance regarding genomics applications

### Scientific Areas

Bioinformatics, Diagnostic Testing, Drug Safety/Efficacy, Microbiology, Statistics.

Examples of Strategic Opportunity

- “Detailing” of staff into laboratories/operational settings, or planned industry “show-and-tells” to get real-time knowledge/experience in evolving technologies, resulting in more informed reviews.
- Educational site visits by staff to manufacturing and industrial development sites to gain experience in production modalities, quality control activities, etc.
- If we had the necessary models, standards, databases and other infrastructure resources, FDA would be able to provide timely input to sponsors regarding diagnostic devices and drug-related applications.
- Participation in standards-setting organizations would help drive standards towards materials and methods useful in the regulatory setting, and provide confidence in use of genomics methods through application of well-understood quality control materials, methods, and metrics.
- Development of new guidances to clearly interpret regulations and communicate FDA thinking would aid manufacturers in understanding and meeting the regulatory requirements in a least burdensome manner.

## ADVERSE EVENT DETECTION, DATA, AND ANALYSIS—CDRH #8

### Current State

Data on device adverse events comes largely from reports from individuals and institutions. The data received can be severely limited in important ways: information is often incomplete, inaccurate, not reported in standard ways, not timely, etc. Statistical tools are rarely used in the identification of signals in voluntary reporting systems or in the data-mining of registries and other rich databases.

We also do not have “denominator” data related to medical errors with medical devices, which complicates the ability to conduct useful analyses. CDRH does not have access to population-based clinical databases for observational study of device issues, and even the more sophisticated of these databases often do not routinely capture device-specific information. As a result, analysis of post-market safety issues can be sub-optimal.

Although some CDRH AE systems are electronic, these are not integrated with other CDRH systems, and similarly cannot adequately communicate with data sources of other agencies (such as the Veterans Administration and the Centers for Medicare and Medicaid Services) that may have important information on device safety.

Inadequate access to adverse event data sources or the tools for effective analysis is compounded by the lack of a unique identification system for medical devices, this situation seriously limits the capability for signals detection and the provision of actionable intelligence.

### Scientific/Technical Limitation

Perhaps the most important current limitation on appropriate medical device surveillance, risk assessment and related activities is lack of a consistent, standard, unique device identifier system. As a result, the relevant data are captured and organized inconsistently. For example, while FDA maintains numerous databases and reporting systems related to medical devices, within these databases, significantly different devices are linked to the same category (e.g., FDA Product Code), or different categories are used to index information on the same device.

The second key limitation in this area is the lack of advanced data mining and analysis tools and resources to develop more active surveillance and signals detection approaches, and the absence of data bases to support such work.

Additional important scientific and technical limitations in this area include:

- lack of resources to access population-based data, and the experts to develop appropriate algorithms to mine that data.
- lack of systems that can support sophisticated manipulation of the data, linking to other important sources of safety data, and timely or problem-free review of the data.
- lack of a unique identifier system for tracking medical devices throughout their life cycle
- lack of use of Medical Products Safety Device Network programs

Tools are not fully developed for the large databases nor has the quality of many databases merited sophisticated statistical data-mining.

#### Scientific Area

Engineering Sciences (Information Technology, Electronics, Device Technology), Epidemiology, Informatics.

#### Examples of Strategic Opportunity

Use of automatic identification technologies for medical devices could improve device safety, for example, we will be able to perform more accurate analysis of adverse events; and improve the quality of care for patients by reducing medical errors, facilitating device recalls and predicting clinical risks.

Access to population data bases and sophisticated tools for passive surveillance would enable CDRH to develop safety information that could improve the quality of care for patients, reduce medical errors, and facilitate device recalls. Such information could also feed back into improved clinical trial designs.

Communication and collaborate with the community the need to incorporate this information, even if initially confined to certain device areas, such as implantable devices. These things are possible if there funding similar to those used to support drug safety funding (e.g., user fees for post-market surveillance).

## **NANOTECHNOLOGY—CDRH #9**

### Current State

The science, technology and commercial applications of nanotechnology (NT) are expanding at a rapid pace. Industry, academia, and government funding agencies are making significant advances in the development of processes/products to integrate nanoscale components into devices. Applications of NT products are emerging in surgery, cancer diagnosis and therapy, bio-detection of molecular disease markers, medical imaging, tissue engineered products, and devices for drug delivery.

### Scientific/Technical Limitation

NT is expected to present an increasing array of new materials where nanoscale properties are relevant to safety and efficacy reviews and in some cases, we may lack validated methods to fully characterize the relevant physical, chemical, surface chemical and biological properties of NT applications, and robust models for predicting the potential impact of NT on human health (including methods/systems to evaluate the Total Product Life Cycle to assess health effects).

### Scientific Areas

Chemistry, Microbiology, Nanoscience (Nanotechnology, Nanometrology), Physics.

### Examples of Strategic Opportunity

Improved science in this area would support:

- Standards and guidances to help product sponsors develop safer products, and to provide the certainty needed to remove barriers to innovation and technological development.
- Development of risk management approaches for introduction of NT products into the medical device field that ensure safety to patients as well as maximize benefits to patients in a shortest time period.

## **HUMAN FACTORS—CDRH #10**

### Current State

Medical devices are becoming increasingly complex and computerized, and are increasingly used in settings outside the hospital/healthcare facility by those with limited training. This increases the risk of device failure/misuse connected to the actions of the user. Manufacturers should be giving considerably more attention to human factors during the design of devices, during the validation of those designs and in their instructions for use.

### Scientific/Technical Limitation

The general lack of Human factors expertise ( applied psychologists and engineers certified in human factors field), lack of industry adaptation of international standards, appropriate design controls in manufacturing are some reasons for failure of devices from human errors. Some examples of recent device failures are infusion pumps and anesthesia gas machines. These devices experienced adverse events resulting from use of non-standard methods to control fluid flow. These events could have been avoided by human factors standards that require detailed instructions, design changes, multiple interlock/alarm mechanisms, etc.

### Scientific Area

Engineering Sciences (Systems Engineering, Human Factors Certification), Physicians (Applied Psychologists with Human Factors Expertise).

### Examples of Strategic Opportunity

More robust medical devices with fewer failures due to human factors can be designed by following international standards that take into consideration of human factors and other design features to avoid adverse events.

Promote the use of standards so that devices perform satisfactorily in practice and produce fewer adverse events.

## CLOSED LOOP SYSTEMS—CDRH #11

### Current State

More and more medical devices are integrated into closed loop systems where diagnostic and therapeutic devices are integrated. These systems both measure a parameter of interest and then use this measurement in sophisticated computer control algorithms to deliver therapy. The artificial pancreas, a combination of a continuous glucose monitor and an insulin delivery pump, is one such example.

### Scientific/Technical Limitation

Today, we lack key supporting science to guide the development of and assess the safety and efficacy of such systems. Key areas of scientific and technical limitations include:

- the absence of well-understood and validated safety measures
- the absence of well-understood and validated efficacy endpoints
- the absence of well-understood methods for diagnosing failure of such integrated systems.
- insufficient data handling/storage capacity of devices
- establishing robust software algorithms to ensure safe use under real world conditions

### Scientific Areas

Engineering Sciences (Systems Engineering, Computer Technology, Software Engineering).

### Examples of Strategic Opportunity

Ability to diagnose integrated device failures, and adequate safety measures to prevent risk to patients. With reliable measures of safety and efficacy measures, CDRH could better evaluate experimental systems such as the closed-loop artificial pancreas (linked continuous glucose monitoring and insulin pump), and provide guidance that would provide the clarity on scientific expectations needed to promote development of these products.

Participation in standards development would help drive standards towards materials and methods that will be useful in the regulatory setting and provide confidence in use of integrated devices.

Development of new guidances to clearly interpret regulations and communicate FDA thinking would aid manufacturers in understanding and meeting regulatory requirements in a least burdensome manner.

## COMBINATION PRODUCTS—CDRH #12

### Current State

Stakeholders report that FDA can expect to receive significantly more combination products for review as technological advances continue to merge therapeutic products and blur the historical lines of separation between FDA's medical product Centers. Combination products often involve cutting edge, novel technologies (tissue engineered products, drug eluting stents) that raise unique scientific and technical issues.

### Scientific/Technical Limitation

- The combination of two distinct components introduces additional scientific factors to consider in the formulation of appropriate regulatory requirements. An example is a drug eluting stent where the drug used takes a variety of forms and its mechanisms of action differ based on the product.
- Manufacturing and GMP issues are unique to these products. Since these are complex products that require the application of different unit operations, where each operation is governed by a different set of quality system requirements.
- Safety evaluation of combination products incorporating novel technologies. There is a general lack of information on the mechanistic understanding of the action of different products in the combination device, to ensure that all relevant issues are addressed, without imposing unnecessary burden on regulated industry.

### Scientific Area

Life Sciences, Physical Sciences.

### Examples of Strategic Opportunity

If CDRH could develop an improved understanding of the appropriate level of testing to ensure the safety and mechanism of action of these combination products, their entry into the market could be faster and minimize post-market issues. In addition, the development/evaluation of preclinical models for combination products incorporating medical devices would minimize barriers to entry of novel products.

## MEDICAL IMAGING AND COMPUTER-AIDED DIAGNOSIS—CDRH #13

### Current State

Among other advances, personalized medical imaging is evolving such that, given appropriate information about the patient, for example, a “virtual cath lab” can select the best set of imaging parameters for a specific imaging task for the specific patient, leading to reduced risk (from the ionizing radiation) and improved diagnosis and/or therapy.

Computer-aided diagnosis (CAD) devices are increasingly being used in clinical medicine leading to the need for the development of measures of true clinical utility. Typically, these devices have been developed and evaluated using only a limited data set that does not necessarily represent clinical use.

Medical imaging is now estimated to contribute more than half the population exposure to ionizing radiation (up from 15 percent 20 years ago) and the individual doses are such that a significant number of cancers are likely to result.

### Scientific/Technical Limitation

Today, we lack robust and validated computer models for optimizing imaging parameters, and models of anatomically and physiologically accurate virtual circulatory and other systems. The absence of large, well-characterized clinical data sets for CAD development and evaluation, and the current limited understanding or assessment of algorithm stability, are limiting FDA’s ability to develop optimum parameters.

There is a clear lack of detailed and up-to-date picture of exposures in the US and this gap is particularly important in high dose procedures like CT. The picture we have from NEXT does not cover all the dose-intensive procedures, cannot sample frequently enough to characterize rapidly evolving imaging practices and is based on a relatively small sample. An ongoing comprehensive national database of medical imaging dose needs to be established.

### Scientific Areas

Mathematical Modeling, Physicians, Physics.

### Examples of Strategic Opportunity

Such models would allow selection of optimum imaging parameters by the physicians to enhance outcome of patient diagnosis and therapy.

In addition, facilitating the development of public data sets, clinical study of CAD, and the development of stability metrics for these devices would promote patients safety and accuracy in diagnosis.

In addition, if we had a comprehensive national database of medical imaging dose needs, we could decrease the number of cancer caused by overexposures.

## Center for Drug Evaluation and Research (CDER)

### PREDICTIVE PRE-CLINICAL SAFETY MODELS—CDER #1

#### Current State

FDA utilizes the results of animal toxicology studies as screening tools prior to initiation of human clinical trials to assess safety.

#### Scientific/Technical Limitation

Our knowledge of the positive or negative predictive value of animal toxicology studies is limited.

#### Scientific Areas

Biochemistry, Bioinformatics, Cell Biology, Clinical Pharmacology, Developmental, Genetics, Immunology, Mathematics, Medicine, Molecular biology, Neuroscience, Pharmacology, Physiology, Panomics, Pathology, Toxicology.

#### Examples of Strategic Opportunity

More work to better characterize how to obtain the most data from toxicology studies and better understand their findings in relation to humans is a challenge that we expect to grow with our continued focus on drug safety. There are a number of opportunities to make substantive progress in this area through the use of strategic partnerships and collaborative efforts. One such effort is the Predictive Safety Testing Consortium. This group will focus on identifying preclinical biomarkers as predictors of human safety in areas such as nephrotoxicity, hepatotoxicity, and vasculitis. The strategic opportunity is to engage a large, cross-cutting consortium of federal, industry and academic scientific expertise to identify and validate potential biomarkers. The development of more predictive safety biomarkers would improve the effectiveness of safety screening prior to introducing products into humans and help target toxicity monitoring in early trials.

FDA's files constitute the world's largest repository of in vitro and animal results that are linked with actual human outcomes data. Further data mining efforts that effectively protect proprietary data can be utilized to develop predictive safety models to aid in the evaluation of human safety from existing animal data using structure activity principles.

## **INTEGRATING GENOMICS INTO REGULATORY ACTIVITIES—CDER #2**

### Current State

New genomic technologies hold great promise as powerful biomarkers. Some in vitro diagnostic tests that detect specific genetic variations that affect an individual's response to treatment are ready for use.

There is much interest in pharmacogenomics and related scientific disciplines among basic scientists at FDA. More importantly, there remains a gap between the use of pharmacogenomics in drug development and its practical application in the regulatory work at FDA.

### Scientific/Technical Limitation

Regulatory scientists must gain experience with genomic data to better understand how it can be evaluated in the context of other data to inform regulatory decision making. Furthermore, as this field continues to evolve, keeping regulatory scientists abreast of new applications of this technology is critical. There is a critical need to further develop:

- The types of genetic loci for pharmacogenomic testing
- The test systems and techniques employed
- The problems encountered in applying pharmacogenomic tests to drug development
- The ability to transmit, store, and process large amounts of complex pharmacogenomic data streams
- Standards for genomic analysis

### Scientific Areas

Bioinformatics, Cell Biology, Chemistry, Clinical Pharmacology, Developmental, Epidemiology, Genetics, Immunology, Mathematics, Medicine, Molecular biology, Neuroscience, Panomics, Pathology, Pharmacology, Physiology, Toxicology.

### Examples of Strategic Opportunity

One of the major opportunities for increasing both knowledge of the predictive value of genomic data and the experience of FDA reviewers is the Voluntary Genomic Data Submission (VDGS) process. VGDSs are a novel way to share pharmacogenomic data that are of an exploratory or research nature in an informal setting without regulatory decision-making. In this way, voluntary submissions benefit both the industry and the FDA by providing a means for sponsors to ensure that regulatory scientists are familiar with and prepared to appropriately evaluate future genomic (and other novel biomarker-related) submissions. The opportunity is for FDA and industry scientists to incorporate understanding of how to best utilize genomic data to enhance regulatory decision making.

**UNDERSTANDING THE GENETIC BASIS OF SERIOUS ADVERSE EVENTS—CDER #3**Current State

Interpretation of post-marketing safety data is complex, involving analysis of post-approval clinical data, detailed review of adverse drug experience reports in the context of relevant clinical studies, estimates of drug usage and adverse drug experience reporting rates, estimates of background rates of the adverse event, and other relevant information.

Scientific/Technical Limitation

The science of drug safety needs to go beyond review of spontaneous adverse event reports, active surveillance, and pharmacoepidemiological studies. Other disciplines, such as pharmacogenetics, need to be integrated into the assessment of safety. The rarity of Serious Adverse Events (SAEs) makes it difficult to accrue enough cases and controls to conduct an adequate study. Furthermore, identifying and obtaining well-phenotyped adverse event cases and controls for assessment of SAEs using a common platform for evaluation is challenging.

Scientific Areas

Bioinformatics, Clinical Pharmacology, Epidemiology, Genetics, Immunology, Mathematics, Medicine, Molecular biology, Panomics, Toxicology.

Examples of Strategic Opportunity

One example of an opportunity in this area is the Serious Adverse Event Consortium formed with the purpose of identifying DNA-variants which are clinically useful in assessing the risk of serious adverse events, such as Stevens Johnson syndrome and Drug Induced Liver Injury. FDA is acting in a scientific advisory role to this SAE consortium. These types of approaches offer an opportunity for development of personalized medicine by identifying patients who may develop potentially serious adverse events prior to initiation of therapy.

## **INNOVATIVE CLINICAL TRIAL DESIGNS—CDER #4**

### Current State

The majority of clinical trials currently conducted during product development, particularly for pharmaceuticals, are empirical.

### Scientific/Technical Limitation

Empirical clinical trials have a limited ability to address more than a few questions within a single trial. Consequently, after an extensive development program, numerous questions about product performance frequently remain unanswered. Guidance is also needed on when it is valid to make changes to a clinical trial protocol, based on early or interim study results. Furthermore, in many diseases, more than a single efficacy endpoint may be of importance. All clinical research studies experience some level of subject attrition, ranging from a few patients to more than half of the study subjects. Patients lost to follow-up pose a particular challenge for analyzing trial outcomes.

### Scientific Areas

Clinical Pharmacology, Epidemiology, Mathematics, Medicine.

### Examples of Strategic Opportunity

In order to enhance the development of new and beneficial drugs, stakeholders need clarification on appropriate methods for handling these clinical trial design issues. FDA can work in collaboration with outside stakeholders to explore the science of these issues (via workshops or other public meetings). Further, these efforts may lead to the development of guidance in the following areas:

- Adaptive trial designs
- Treatment of missing data
- Non-inferiority Trials
- Multiple endpoints
- Enriched trial designs

## **PREDICTIVE ANIMAL MODELS FOR TESTING BIOTERRORISM COUNTERMEASURES—CDER #5**

### Current State

With increasing challenges of bioterrorism, animal models are used to predict countermeasure effectiveness in humans.

### Scientific/Technical Limitation

Since human studies would be unethical (deliberate exposure of humans to life threatening illnesses) or infeasible (e.g., field testing of smallpox vaccine is not possible because smallpox has been eliminated as a natural disease), development of relevant and predictive animal models is needed.

There is a lack of data and studies on the efficacy of medications already approved by FDA for other indications, for use as medical countermeasures.

### Scientific Areas

Epidemiology, Genetics, Immunology, Mathematics, Medicine, Microbiology, Molecular biology, Pathology, Pharmacology, Toxicology, Veterinarian.

### Examples of Strategic Opportunity

FDA and its partners can play a role in both developing such models and helping to define appropriate and efficient pathways for their use in product development. Such efficiency is critical both for effective utilization of often limited or ethically sensitive animal resources, as well as ensuring reliable threat preparedness in a timely manner.

Additional utilization of these models will provide the data needed to determine efficacy and gain approval for additional indications for already approved medications, providing an increased pharmacologic arsenal for counter-terrorism.

## IDENTIFICATION AND QUALIFICATION OF BIOMARKERS FOR SAFETY AND EFFICACY—CDER #6

### Current State

Biomarkers are potentially useful indicators of a drug's performance (e.g., preclinical safety, serious adverse events, disease progression, therapeutic responsiveness, metabolic variability). Biomarkers have often been developed independent of an intended use for guiding drug development.

### Scientific/Technical Limitation

Many of the biomarkers used in medical product development today have been in use for many years, even decades. These longstanding biomarkers were empirically derived and often lack predictive and explanatory power. A large number of potential new biomarkers have been proposed, but the essential work needed to evaluate their utility for their intended use, known as biomarker qualification, remains.

### Scientific Areas

Biochemistry, Bioinformatics, Cell Biology, Chemistry, Clinical Pharmacology, Developmental, Epidemiology, Genetics, Immunology, Mathematics, Medicine, Molecular biology, Neuroscience, Pharmacology, Physiology, Panomics, Pathology, Toxicology.

### Examples of Strategic Opportunity

Each biomarker must be qualified for its intended use prior to regulatory acceptance. To compress research and development of new biomarkers into a timescale of years, a collaborative approach is necessary. A number of pooled efforts which involve multiple sectors in the healthcare research and development system have been initiated in a number of areas, from preclinical safety testing to post-market safety. FDA reviewers will need to participate in the design of the definitive studies intended to qualify the biomarker for a specific regulatory use. FDA expertise will be needed on an ongoing basis in the effort to determine protocols for the selection and testing of candidate biomarkers for qualification.

- The Biomarkers Consortium was launched in October 2006 to facilitate identification and clinical qualification of biomarkers. This Consortium is a public-private biomedical research partnership supported by the Foundation for the National Institutes of Health. (FNIH). FDA is acting in a scientific advisory role to this consortium.
- 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.
- CDER is piloting a process for qualification of biomarkers

- FDA and Novartis are collaborating, via a CRADA, on the identification of nephrotoxic biomarkers that predict the effects of drug compounds on kidney function.
- The Cardiovascular Drug Safety and Biomarker Research Program is a collaboration between the FDA, the Critical Path Institute (C-Path) and the University of Utah to establish an evidence-based framework for determining the clinical utility of cardiovascular biomarkers, including genetic variants that determine the anticoagulation response to warfarin. The opportunity is to develop a pharmacogenetic algorithm to personalize warfarin dosing to improve the therapeutic efficacy and safety of dosing.
- FDA is partnering 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 over 500,000 ECGs. The large database will allow targeted studies to capture information useful for pre-market evaluation of drug safety by helping to distinguish drugs with the potential to cause fatal cardiac arrhythmias.
- The Oncology Biomarker Qualification Initiative (OBQI), is a collaborative effort between the FDA, National Cancer Institute (NCI), and the Centers for Medicare and Medicaid Services (CMS) to create a framework for collaboration to qualify cancer biomarkers that can be useful in research, developing diagnostic tests, medical product quality assessment, and evidence-based decision-making.
- 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.
- A new consortium, the Severe Adverse Events (SAEs) Consortium, 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.

Collectively, these collaborative opportunities to identify and qualify biomarkers for use in predicting safety and efficacy of drugs in development have the potential to improve the effectiveness of safety screening prior to introducing products in to humans, enable better selection of initial human doses, and help target toxicity monitoring in early trials. These biomarkers can also be used to individualize drug dosing to develop more rigorous protocols based on a patient's unique biomarker profile.

## ACTIVE SAFETY SURVEILLANCE—CDER #7

### Current State

Our current post-marketing drug safety system is largely based on a passive, spontaneous system of adverse event reporting. In addition, analysis of pre-market safety data presents a challenge as clinical trials are designed to primarily assess efficacy.

The current post-marketing drug safety system relies on voluntary, spontaneous reporting by health care professionals, consumers, patients, and manufacturers. The system has the advantages that it is broad based, simple, inexpensive and provides signals for early detection of safety signals, especially rare adverse reactions. However, there are a number of limitations, which include:

- Underreporting, which varies from drug to drug and over time
- Variability in quality and completeness of reports
- Gross assessment of event rate
- Numerator uncertain
- Denominator (number of exposed patients) must be estimated

The current pre-market drug safety evaluation relies on extracting safety data from clinical trials generally powered to assess efficacy.

### Scientific/Technical Limitation

We need to modernize how we detect drug safety signals, by developing methods of active surveillance using a variety of data sources to complement our passive surveillance system. Today, we lack:

- Refined and evaluated data mining methodologies, robust and validated methods for active surveillance to prospectively collect and detect drug safety signals, and improved means of completely and accurately measuring prescription and non-prescription medication use by the public.
- robust methods of analyzing healthcare data from large, population-based datasets using the techniques of observational epidemiology (e.g., case-control studies and cohort studies).
- Resources to gain access to the databases and trained personnel needed to develop the methods described above.

### Scientific Areas

Bioinformatics, Epidemiology, Mathematics, Medicine.

### Examples of Strategic Opportunity

FDA has entered into a data use agreement with AHRQ to use data from the Centers for Medicare & Medicaid Services (CMS) to conduct a collaborative research project to develop data structures and methodologies for identifying and analyzing adverse drug events. The study will include three projects involving the use of four drugs in the Medicare beneficiary population. In addition to studying safety issues relating to these specific drugs, the goal of this program is to gain familiarity with CMS data, in anticipation of the availability of Medicare Part D data in the near future. The opportunity provided by these efforts is to develop a more robust approach to identification of post-market safety concerns.

The Quantitative Safety and Pharmacoepidemiology Group (QSPB) has been formed to promote science-based, data-supported, regulatory decisions on the safe use of drugs. This group of internal experts will develop quantitative methods for pre-market safety evaluation, develop and disseminate best practices for reviews of safety aspects of study protocols during product development, and provide consistency in review practices and analytical approaches across review divisions to the extent possible

The potential opportunity for CDER is to develop greater understanding of the role and utility of observational epidemiology studies in assessments of post-marketing safety for regulatory action. These activities will further provide additional evidence based resources to inform regulatory decision making.

## IN SILICO MODELING TOOLS—CDER #8

### Current State

The implementation of FDA's regulatory activities could be enhanced by taking full advantage of modeling and simulation tools to maximize knowledge to be gained from the Agency's vast data repository.

### Scientific/Technical Limitation

FDA has large stores of data from regulatory filings. Much of this data is not archived in databases in such a way that it can be readily extracted, combined with additional data, and used in modeling or simulations. In addition, much available data are not being applied to *in-silico* models of disease that have the potential to inform the drug development process. There are limitations in both IT resources to develop and extract these legacy data and human resources with appropriate scientific expertise to create in silico models.

### Scientific Areas

Bioinformatics, Cell Biology, Chemistry, Clinical Pharmacology, Epidemiology, Genetics, Immunology, Mathematics, Medicine, Microbiology, Molecular biology, Physiology, Software, Toxicology, .

### Examples of Strategic Opportunity

There are numerous opportunities to collect, store, and utilize archival data to develop models which can aid regulatory decision making. The opportunities are wide-ranging and FDA has begun to work in some of these areas, but many opportunities to utilize this data exist.

The FDA has a unique opportunity to build drug-disease models because it has accumulated in its files significant amounts of placebo response data in different disease states and important historical information on missing data and drop-out rates from across many different NDAs. The FDA would like to build drug-disease models for the following therapeutic areas:

- Acquired immune deficiency syndrome caused by the HIV-AIDS
- Parkinson's disease
- Obesity
- Non-small-cell lung cancer
- Type II diabetes
- Osteoarthritis
- Alzheimer's disease

FDA has created large stores of non-proprietary toxicology data. Computational toxicology incorporates this information and applies advances in computer technology and quantitative structure activity relationship (QSAR) methods to screen compounds for potential toxicity. Through the use of several Cooperative Research and Development Agreements, the cumulative data is being applied to the development of databases and structure-activity software that will aid in predicting the toxicity of chemical moieties.

## **RISK-BASED INSPECTIONAL MODELS—CDER #9**

### Current State

FDA is responsible for conducting comprehensive regulatory coverage of all aspects of production and distribution of drugs and drug products to ensure that such products meet regulatory standards. Currently, there are not enough FDA resources to audit every aspect of cGMP in every manufacturing facility during every inspection visit.

### Scientific/Technical Limitation

FDA's resources for regulatory inspections are challenged by a growing number of manufacturing sites and clinical trial sites, including a rapidly growing foreign component. Current database and statistical analysis capabilities limit the full utilization of prior data in applying risk-based models to inspectional activities.

### Scientific Areas

Bioinformatics, Mathematics, Manufacturing, Quality, Software.

### Examples of Strategic Opportunity

FDA has a large repository of inspectional data on manufacturing facilities, processes, product characteristics and quality. The Office of Compliance has an opportunity to build upon its existing databases ranging from drug registration and listings, recalls, drug defect reports, adverse event reporting, etc. Incorporation of statistical analysis tools will aid in the detection of signals for drug quality problems or problems in adverse event reporting relating to drug safety. The ability to utilize cumulative compliance data for building risk-based models to prioritize inspectional activities will be maximize the effectiveness of the Agency's limited inspectional and compliance resources in the face of increasing technical, geographic and product specific challenges.

## BETTER TOOLS FOR PEDIATRIC DRUG DEVELOPMENT—CDER #10

### Current State

A significant proportion of clinical drug trials have failed to show efficacy or clinical activity in pediatric patients despite proven prior evidence of efficacy in adults. Some of the data from these studies have raised new research questions regarding differential drug effects across race/ethnicity, adequacy of assumptions of PK/PD relationships, and dose selection for pediatric clinical trials. Still other findings have raised questions about the appropriateness of study design, selected end points, sample size and duration of pediatric trials.

### Scientific/Technical Limitation

A systematic analysis of data from across various pediatric trials is difficult because the data from these studies have been submitted to the Agency in various non-standardized structures and formats by sponsors. To facilitate meta-analysis across multiple studies, the legacy data that reside at FDA need to be transformed into a uniform standard structure that is CDISC/SDTM compliant. This effort is limited by human and IT resources to appropriately map each of the relevant data domains to the Study Data Tabulation Model (SDTM) format. Further statistical and pharmacologic expertise is needed to assess the meta-analyzed data to better inform dose selection and study population for future pediatric trials.

### Scientific Areas

Bioinformatics, Clinical Pharmacology, Epidemiology, Mathematics, Medicine

### Examples of Strategic Opportunity

The FDA has accumulated the largest number of regulatory submissions of pediatric clinical trial data in the world. Development of a pediatric trials database of electronic datasets converted to standardized format CDISC/SDTM can be imported into a data repository that can be queried. Development of this database will allow systematic review of PK and PD studies from various data submissions and inform the design and conduct of future pediatric studies.

## **SAFETY, EFFICACY, AND CHARACTERIZATION OF COMPLEX BIOLOGIC PRODUCTS—CDER #11**

### Current State

Rapid developments in the rational design of receptor-targeted peptides and proteins, as well as monoclonal antibodies have resulted in their application as therapeutic agents. There are a variety of techniques currently utilized to control production and assess the purity and activity of end products. The variability in manufacturing, product characterization, and biological potency assays may lead to significant variability in product effectiveness and safety.

### Scientific/Technical Limitation

The use of complex proteins and monoclonal antibodies as therapeutic agents poses a number of development and regulatory challenges. Production often relies on the use of cell-based systems, which requires careful removal of adventitious agents and appropriate assays for purity. Subtle post-translational modifications, which may be difficult to control, can affect biologic activity. Furthermore, monoclonal antibodies may be conjugated to therapeutic peptides or small molecules. Characterization of the chemical structure and biologic activity of production lots is challenging. Unwanted immune responses (e.g., serious immune reactions to the therapeutic protein or contaminants or immunogenicity of the therapeutic protein) create difficulties.

### Scientific Areas

Bioinformatics, Cell Biology, Chemical Engineering, Chemistry, Clinical Pharmacology, Immunology, Manufacturing, Mathematics, Medicine, Microbiology, Molecular biology, Pathology, Pharmacology, Quality, Software, Toxicology.

### Example of Strategic Opportunity

The opportunity is to reduce technical uncertainties associated with the development and regulation of therapeutic proteins and monoclonal antibodies by research targeted to a number of areas:

- Better understanding of how production factors affect structural attributes which are critical for determining biologic and immunologic activity.
- Utilizing the quality by design approach to better ensure end products with more consistent structural and biologic profiles.
- Development of predictive assays to quantify both biologic activity and immunogenic potential
- Identifying critical factors which would minimize product immunogenicity

Principles learned during development of these approaches may be incorporated into new guidance, providing a more uniform and predictable environment for the development of therapeutic proteins and monoclonal antibodies.

## **BIOEQUIVALENCE SCIENCE—CDER #12**

### Current State

The number of generic drug submissions is increasing. At the same time, pharmaceutical and biologic products coming off patent are increasingly complex.

### Scientific/Technical Limitation

The bioequivalence of drugs is typically determined by measuring and comparing the pharmacokinetic parameters of the generic to the reference drug. This common approach to the assessment of bioequivalence is not applicable to drugs which act locally (e.g., skin, nasal sprays, GI drugs). Difficulties in providing an acceptable method for demonstrating bioequivalence have presented barriers to the development and approval of some generic drugs.

### Scientific Areas

Bioinformatics, Cell Biology, Chemistry, Clinical Pharmacology, Developmental, Environmental Science, Genetics, Immunology, Mathematics, Medicine, Pharmacology, Physiology, Toxicology.

### Example of Strategic Opportunity

- Collaborative efforts can speed the development and refinement of critical technology and generation of knowledge needed to improve the tools the Agency needs to characterize the chemistry and bioequivalence of generics.
- Studies which identify the relationship of critical manufacturing process parameters to product quality of generic drugs can be applied to the incorporation of quality by design.
- A better understanding of the effects of structural and formulation characteristics on bioequivalence may be aided by modeling approaches built on previous bioequivalence data. This may lead to more efficient approaches to bioequivalence assessment for certain classes of drugs.

## MANUFACTURING SCIENCE—CDER #13

### Current State

Problems in industrialization can be frequent hurdles in drug development, delaying trials, limiting access to products, and sometimes completely blocking development.

### Scientific/Technical Limitation

In the post-market setting, poor product design, inadequate characterization and testing, or poor manufacturing process design can result in problems with product performance or malfunctions. These problems can cause patient injury, regulatory action, recalls, or lack of product availability. In many cases, manufacturers lack the scientific tools to adequately identify and characterize critical product attributes, design well-controlled manufacturing processes, using modern process control technologies, or tightly manage product quality during production. This presents a technical challenge to the FDA, which is responsible for monitoring product quality. The Agency need to generate additional knowledge and information on critical manufacturing attributes which affect final product quality.

### Scientific Areas

Cell Biology, Chemistry, Environmental Science, Immunology, Microbiology, Nanotechnology, Mathematics, Bioinformatics, Industrial Engineer, Chemical Engineer, Manufacturing, Quality, Software.

### Example of Strategic Opportunity

- FDA is developing calibration and validation procedures and appropriate instrument qualification standards for use with 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.
- FDA is working with industry 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.
- Today there is no standard reference method for assessing the distribution of active pharmaceutical ingredient (API) particle size in nasal spray suspensions. FDA is working to refine Raman Chemical Imaging use in aqueous nasally inhaled products. The goal is to develop accepted scientific standards for key characteristics of these products, so sponsors will have greater certainty regarding acceptable product parameters.

These opportunities offer the potential for greater consistency, efficiency and quality in product development and will enhance the ability of the FDA to monitor critical manufacturing parameters, often in real time, to improve regulatory oversight.

## **RISK COMMUNICATIONS—CDER #14**

### Current State

FDA-approved human drug labeling is the primary tool the Agency uses to communicate risk and benefit to the public. In addition, FDA regulates direct to consumer advertising by manufacturers. CDER provides drug safety information to the public through a variety of other risk communication tools including, Patient and Healthcare Professional Information Sheets, Public Health Advisories, Press Releases, MedWatch Safety Updates, and Talk Papers. FDA also conducts educational campaigns and conveys drug safety information through the CDER Internet site.

Once a drug product is marketed, ensuring its safety becomes a complicated responsibility shared by many parties. These include health care professionals (who must weigh both the risks and the benefits of drugs in deciding whether to prescribe a particular drug for a particular patient to achieve an optimal therapeutic outcome); patients and caregivers (who must understand both the benefits and risks of drugs so they can have informed discussions with their health care professionals about their medicines and make informed decisions about their use); manufacturers, and others.

### Scientific/Technical Limitation

- We lack a robust understanding of the communication needs of CDER's external stakeholders, those audiences impacted by our risk or safety communications, to understand their values, attitudes, preferences and behaviors regarding drug safety and drug safety information
- Resources and expertise are needed to fully develop and test an informative evaluation method for assessing the impact of current and newly developed risk communication tools.
- Additional resources and expertise are needed to design and deploy research strategies to better understand consumer comprehension of direct to consumer advertising.

### Scientific Areas

Cognitive Psychology, Risk Perception and Communication, Social Psychology.

### Example of Strategic Opportunity

Targeted research provides a strategic opportunity to improve our understanding of the communication needs of CDER's external stakeholders. Additionally, establishment of a new advisory committee offers the opportunity to obtain input to improve the Agency's communication policies and practices and to advise FDA on implementing communication strategies consistent with the best available and evolving evidence. Patients and consumers as well as experts in risk and crisis communication and social and cognitive sciences will be included.

These strategic opportunities may provide enhanced understanding of how to convey more consistent messages on the risks and benefits of consumer medications.

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## Center for Food Safety and Applied Nutrition

The FDA's Center for Food Safety and Applied Nutrition (CFSAN) views its regulatory activities and, thus, its scientific needs, within a risk analysis framework. This framework has three major components, each dependent upon a dynamic science base:

- Risk Assessment—science needed to define risk
- Risk Management—science needed to develop, decide, and implement risk mitigation programs
- Risk Communication—science needed to facilitate communication on risk and risk management concepts between risk managers and the public and other stakeholders. Risk Communication is a critical element in changing consumer and producer behavior, and, in some instances, the risk communication is intended to bring about this change and yield risk mitigation.

The Center's current scientific needs are extensive and diverse in terms of critical expertise, infrastructure, and knowledge gaps. These write-ups are illustrative, and not intended to capture all of the gaps in science that we have, whether due to resource constraints or scientific limitations. Instead, CFSAN is providing a series of examples that identify critical areas where our scientific base needs to be strengthened through (1) increased scientific expertise, (2) additional resources allocated to the program, or (3) greater leverage of outside expertise from the broader scientific community. It is important to emphasize that in each of these examples, and throughout our regulatory programs, a multi-disciplinary knowledge base is critical and is reflected in our scientific needs. The timeframe associated with these needs is short-term, i.e., within the next 18 months.

## **FOOD PRODUCTION SCIENCES: RISK MITIGATION AT THE SOURCE—CFSAN #1**

### Current State

The food industry is rapidly changing both in terms of its global nature and the sophistication of the technologies used for production, processing, and marketing. In addition, the hazards related to food are changing and evolving in concert with changing technologies and food production locales. The ability of CFSAN to effectively assess and manage food safety and food defense risk is dependent on having detailed information on all aspects of the food industry.

This has become a challenge for food safety issues related to the primary production of food commodities. Mitigation of risk at the food processing step in the food chain has been a primary focus for many years. However, the number of illnesses involving food commodities that receive little or no processing prior to consumption remains too high. We now need a substantial science base and enhanced expertise in food production in a comprehensive way, not just with respect to processed foods. Contamination factors and control measures for microbial contamination at the production level (produce in fields, fish in the waters) are not well understood scientifically and/or not validated, leading to incomplete or ineffective preventive food safety practices and procedures.

### Scientific/Technical Limitation

The food regulatory program lacks sufficient high-quality applied field and laboratory research data to understand the mechanisms of contamination and how to mitigate or eradicate the universe of pathogens involved in the food production process. Additionally, CFSAN scientists are limited in their knowledge of food production, whether in the agricultural or aquacultural aspects of food production, especially in foreign production arenas. This is a serious impediment to the US food safety program development and adaptation to evolving risk as well as to FDA's ability to play a leadership role or work effectively in concert with international standard setting and harmonization efforts.

### Scientific Areas

Horticulture, Environmental Sciences, Microbiology.

### Examples of Strategic Opportunity

A comprehensive approach to understanding the risks, evaluating the route of contamination, and developing risk management prevention strategies at the production (versus processing) level will yield validated "best practices"; this will mitigate the risk and reduce illness from consumption of minimally processed products. Microbiological safety of fresh and fresh-cut produce and the presence of antibiotics in imported fish are just two of many recent examples of high priority food safety events that CFSAN responded to and that required the Center to have sufficient knowledge of primary production solutions.

## CONSUMER UNDERSTANDING OF NUTRITION AND FOOD SAFETY INFORMATION— CFSAN #2

### Current State

One of the most important tools that the Center has to enhance both consumer nutrition and consumer safe handling and storage of food is the information provided on the label. However, to effectively convey information to consumers, these labels must be based on a sound understanding of the scientific concepts for effective communication, such as knowledge about the socio-demographic and psychological factors affecting motivation and behavior of different segments of consumers.

### Scientific/Technical Limitation

Knowledge about how best to communicate safety and nutrition information to different audiences must be developed through well-designed studies. Study results must be evaluated and applied by experts in behavioral and social sciences, who can assess the validity and meaning of research results and translate that into practical approaches to food labeling and other communications. The key limit in this area today is the small number of CFSAN staff with scientific expertise in the social and behavior sciences who can design and interpret consumer studies, and insufficient resources and tools needed to evaluate the effectiveness of labeling and nutrition education strategies. The same holds true for new consumer guidance, outreach and educational material as it is developed, tested, and implemented in the consumer marketplace. Another key issue is the time it takes to get a study done from design to interpretation phase.

### Scientific Areas

Education, Psychology, Risk Communication, Sociology, Economics.

### Examples of Strategic Opportunity

The following are examples of areas in which CFSAN needs improved risk communications knowledge and expertise immediately:

- How best to communicate nutrition information to adolescents through food labels
- How best to communicate information to a general audience on making decisions that will result in a healthy total diet, for example by making effective use of calorie and serving size information on the nutrition facts label.
- Investigation of consumer understanding and ability to use possible changes to the nutrition facts panel, as well as front panel statements, claims, and symbols.
- How best to communicate effective safe handling instructions on the labels of fresh-cut produce.
- How best to communicate information about allergens to susceptible individuals through more meaningful label messages, to enhance consumer protection from food allergens (and thus implementation of the Food Allergen Labeling and Consumer Protection Act)

## **REGULATORY PROGRAMS TO IMPLEMENT THE FOOD ALLERGEN LABELING AND CONSUMER PROTECTION ACT (FALCPA) AND ADVANCING EFFECTIVE INTERVENTIONS—CFSAN #3**

### Current State

The inadvertent consumption of food containing proteins to which sensitive consumers are allergic is a significant and increasing public health problem. This threat to public health has been well recognized by FDA. Congress imposed certain requirements on the Agency with the recent passage of the “Food Allergen Labeling and Consumer Protection Act” (FALCPA). Successful implementation requires the enhancement of our scientific resources in terms of assessing the risks posed by food allergens, managing those risks through effective regulatory programs, and communicating those risks through effective labeling and outreach. Increased scientific knowledge and expertise is particularly critical in several areas: methods for the accurate detection of allergen levels in food — to determine levels associated with particular formulations and processing techniques and resulting from inadvertent cross-contact which contaminates products with a food allergen; the determination of “safe” levels (i.e., thresholds) of allergens in foods that can be consumed without risk by sensitive populations; and effective adverse event reporting that allows for timely identification of changes in population sensitivities and emergence of other priority food allergens.

### Scientific/Technical Limitation

The Center’s scientific needs in the areas identified above involve shortfalls in both scientific expertise and data, including data needed for risk assessment. CFSAN needs better understanding of and access to data on the size and sensitivities of the allergic population for each of the allergens identified in FALCPA, especially with regard to allergen doses and distributions impacted by current food processing practices. In conjunction with the required data, CFSAN needs sufficient in-house expertise to review petitions and notifications within the regulatory time limits inherent in FALCPA. Moreover, CFSAN needs to keep up with and implement the advancing scientific methodology needed to accurately detect and assess the biological activity of food allergens. This is necessary not just at the headquarters level, but in the FDA field as well to ensure that we can make scientifically sound regulatory decisions when assessing compliance by the industry. Based on this foundation of cumulative scientific knowledge, supplemented by information about consumer understanding and behavior, effective public health interventions including effective labeling guidance can be developed and implemented.

### Scientific Areas

Chemistry/Biochemistry, Epidemiology, Food Sciences (Consumer Safety Officers), Immunotoxicology, Medical Sciences, Risk Assessors, Risk Communicators, Statisticians.

### Examples of Strategic Opportunity

National and international discussions continue with regards to the science of assessing and establishing allergen thresholds. These important discussions include the appropriate design of clinical trials; standardization and validation of food allergen test

methods including test kits; assessment of the effects of processing and genetic engineering techniques on allergenicity of foods, the use and implementation of effective labels, and the use of labeling icons. It is critical for CFSAN to engage in and influence those discussions by having our scientists and medical experts integrally involved.

Scientific understanding of food allergies and intolerances is progressing rapidly. Examples of time-sensitive strategic opportunities that require the availability of the expertise identified above are:

- The development of guidance describing the scientific data and evidence necessary via notification or petition for exempting an ingredient from the FALCPA allergen labeling requirements.
- The finalization of the "gluten-free" regulation required by FALCPA and proposed by FDA January 23, 2007) so that it provides a scientifically sound, public health-based threshold that is protective of consumer health while allowing maximum options for safe food choices.
- Establishing specific strategies to address cross-contact in processing and retail environments, the appropriate use of advisory labeling, and development of cost-effective, validated testing methods for allergen detection in foods.

## DETECTION OF FOOD-BORNE VIRUSES—CFSAN #4

### Current State

Barely a day goes by without a press report of an outbreak of viral gastroenteritis aboard a cruise ship or at a local restaurant. Food-borne viruses are emerging as the most common cause of food-borne disease. However, our ability to develop effective regulatory programs and guidance is severely hampered by our limited scientific knowledge and resources related to the identification of food-borne viruses and the ability to rapidly diagnose and investigate food-borne outbreaks.

### Scientific/Technical Limitation

During the past 10 years CFSAN has recognized the emerging threat of food-borne viral diseases and has expanded its efforts against this threat by leveraging activities and modest increases in its scientific expertise and infrastructure. However, our ability to enhance our food virology program has not kept pace with the emergence of this public health threat. CFSAN has several critical issues to deal with in this area:

- Detection of food-borne viruses—lack of suitable or established cell culture methods for several important food-borne viruses ; development and application of both sequence-based and functional genomics for broad-based detection of multiple virus strains/species within the same genus as well as viruses within the different families.
- Techniques for genetic fingerprinting of food-borne viruses for outbreak investigations and traceback — development and application of a panomics approach for broad-based detection and identification of multiple virus strains/species.

### Scientific Areas

Food Sciences, Genetics, Molecular Biology, Virology/Microbiology.

### Examples of Strategic Opportunity

Recent advances in methods for viral extraction and analysis using qRT-PCR (quantitative reverse transcription polymerase chain reaction) make it possible to rapidly detect viruses in foods and clinical samples with significant improvements in sensitivity. The development of panomic approaches for virus detection (e.g., genomic identification via the application of multiplex PCR followed by oligonucleotide microarray hybridization) has the potential to provide more information on the identity of multiple virus species than currently possible using an RT-PCR format alone. These detection capabilities, however, do not distinguish infectious from non-infectious (i.e., inactivated) viral particles, and culture of recovered viruses is required for confirmation

of infectivity. Several important food-borne viruses lack suitable cell culture methods for rapid detection of virus replication (e.g., wild-type hepatitis A virus) or are non-culturable (e.g., norovirus) using conventional cell culture techniques, which precludes confirmation of infectious viral risk or exposure. New *in vitro* methods for differentiation of intestinal cell lines and the establishment of virus-like particle producing cell lines have shown promise for the propagation of previously "non-culturable" viruses. Investigating the effects of virus infection on cellular macromolecules to define the viral and cellular events in an appropriate food-borne virus-cell culture model system (e.g., cell culture adapted laboratory strains of hepatitis A virus) may provide a measure of, or marker for, virus replication. The assessment and validation of these recent methods by Center scientists provide opportunities for CFSAN to produce information and data required for the various facets of risk assessment, risk management, risk mitigation, and outbreak investigation/traceback strategies.

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## PREVENTION AND DETECTION OF FOOD-BORNE VIRAL DISEASES—CFSAN #5

### Current State

Barely a day goes by without a press report of an outbreak of viral gastroenteritis aboard a cruise ship or at a local restaurant. Food-borne viruses are emerging as the most common cause of food-borne disease. However, our ability to develop effective regulatory programs and guidance is hampered by our limited scientific knowledge and resources related to the effectiveness of prevention and risk mitigation strategies, and the effectiveness in decontamination of a food facility after it has been involved in a public health incident.

### Scientific/Technical Limitation

During the past 10 years CFSAN has recognized the emerging threat of food-borne viral diseases and has expanded its efforts against this threat by leveraging activities and modest increases in its scientific expertise and infrastructure. However, our ability to enhance our food virus response capacity has not kept pace with the emergence of this public health threat. CFSAN has several critical issues to deal with in this area:

- Effectiveness of food processing and preparation techniques to inactivate food-borne viruses.
- Early identification of infected and asymptomatic food workers.
- Decreasing the risk of food-borne virus transmission from infected food workers at the food service and food retail level.
- Availability of scientifically sound information and decontamination techniques that FDA could provide after an outbreak to ensure that food facilities have been adequately decontaminated. Assays for demonstrating adequate decontamination would be dependant on outcomes of research on Detection of Food-Borne Viruses, described in CFSAN #4.

### Scientific Areas

Food Sciences, Consumer Safety Officers, Medical Sciences, Molecular Biology, Virology/Microbiology.

### Examples of Strategic Opportunity

New science (see CFSAN #4, Detection of Food-Borne Viruses) could provide opportunities for CFSAN to produce information and data required for the various facets of risk assessment, risk management, risk mitigation and outbreak investigation/traceback strategies.

This area is likely to receive increasing attention from the medical community and growing concern among consumers because of greater national and international visibility of food-borne outbreaks and the extent of imported food consumption. Several studies are likely to be released by CDC in the near future that will clearly emphasize the importance of food-borne viruses. This will be further amplified by concern over the role that foods could play in transmission of pandemic viruses and their potential as agents that could be used to purposefully contaminate the food supply.

## SAFETY OF COSMETICS—CFSAN #6

### Current State

The majority of the population (males and females) applies a variety of cosmetics every day. The widely held assumption is that these cosmetic products are safe. Cosmetics include a wide variety of products, including skin moisturizers, perfumes, lipsticks, fingernail polishes, eye and facial makeup preparations, shampoos, hair straighteners, hair colors, toothpastes, and deodorants as well as an even wider variety of individual ingredients in cosmetics. The cosmetic industry is also rapidly undergoing significant changes as the technologies underlying these products are becoming increasingly sophisticated, the manufacturing base becoming more global, and as industry actively explores new “ingredients” and technologies. For example, one of the greatest applications for the emerging science of nanotechnology is in cosmetics. Another example has been the expansion of colors used for tattoos and the explosion in the numbers of people who have tattoos, particularly young men and women.

It is essential that the regulatory philosophy and policy for cosmetics advance together with the science. Rapidly evolving areas of science and technology, including the examples described below, are driving a need to re-examine the framework for safety substantiation and evaluation of cosmetics.

### Scientific/Technical Limitation

These changes are happening at a time when CFSAN’s expertise in cosmetics chemistry, toxicology, and other critical disciplines has been ebbing as a result of retirements and resource limitations.

A good example of the challenges we face is in the evaluation of nanotechnology applications in the cosmetic industry. CFSAN scientists have developed expertise in this broad and rapidly evolving area in order to evaluate products that are already being introduced in the marketplace, but our current cadre is small. Although the Center has received some assistance from scientists in other FDA product centers, the need for an understanding of the unique chemistries and applications associated with cosmetics has limited the extent to which we are able to draw on those resources to meet the needs of the cosmetics program. This surge of interest in nanotechnology also comes at a time when the research infrastructure in dermal toxicology has been severely constricted due to resource limitations. There is also a general need for alternative methods for evaluating this technology, and expanding the Agency computer databases and other systems for storing and analyzing the large data sets generated.

Tattoos, which have come more into the mainstream of consumer use in recent years, represent another area of scientific and regulatory challenge. One of our most critical needs in this arena is for a greater array of analytical methods for characterization of tattoo inks, many of which have not been well-characterized, and their contaminants. To meet this need, our cadre of colors chemists and other scientists well-versed in color technology will need to be expanded. There is also a need for more extensive photolysis studies than have been conducted to date. The data from these studies of tattoo inks are needed to establish safe conditions for their use, including their potential removal.

The availability of relevant expertise is particularly critical because, while under existing regulatory authorities the cosmetic manufacturers have the responsibility to substantiate the safety of their products, CFSAN has the burden of proving that, for example, a contaminant renders a cosmetic possibly injurious to health if the government wishes to remove the cosmetic from the marketplace.

Advances in the overall post-market cosmetic safety program are also highly dependent on the availability of effective adverse event reporting to enable timely identification of emerging problems and prevention of emerging public health threats.

#### Scientific Areas

Physician, Statistician, Chemistry, Dermal Toxicology, Dermatology, Informatics (e.g., QSAR), Materials Science, Life Sciences.

#### Examples of Strategic Opportunity

The highly interdisciplinary nature of the work in cosmetics offers a wealth of scientific opportunities and challenges. We have sought, whenever possible, to leverage with scientific resources both internal and external to the Agency when dealing with issues associated with emerging technologies or cosmetic product components. For example, the mobilization of a general FDA interest group for nanotechnology has established a very useful forum for information exchange which has been of benefit for the FDA cosmetic safety program.

It is essential, however, that the CFSAN cosmetic safety program maintain sufficient expertise and resources to both contribute to and take the fullest advantage of such leveraging efforts.

## **ADVERSE EVENT REPORTING AND ANALYSIS—CFSAN #7**

### Current State

The current adverse event reporting system is a passive, voluntary surveillance system, in which the data available to CFSAN depends on the willingness of consumers, clinicians and others to report adverse events to us.

### Scientific/Technical Limitations

Voluntary surveillance, primarily at the consumer level, limits access to adverse event data.

- This system provides limited data, and limits our ability to perform analysis and trending of dietary supplement adverse events experienced by consumers.
- There are also limitations related to timeliness of access to data, identification of target products, and data analysis issues.

### Examples of Strategic Opportunity

Improving passive surveillance. The Dietary Supplement and Non-Prescription Drug Consumer Protection Act, Public Law 109-462 amends the Federal Food, Drug and Cosmetic Act to require the reporting of “serious” adverse events for both over-the-counter (OTC) drugs and dietary supplements to the US Food and Drug Administration (FDA). This was a change to the FD&C Act, not to the Dietary Supplement Health and Education Act (DSHEA). The new law is self-executing and takes effect on December 22, 2007.

- Mandatory adverse event reporting on dietary supplements from manufacturers is expected to provide substantial increases in adverse event data from dietary supplements (although the system will continue to be based on passive surveillance).
- In addition, new statistical methods have been developed for signal detection.

The capacity for active surveillance would dramatically enhance our understanding of food-related adverse events. For example, for food allergies, if there were robust clinical data bases that we could mine, we could have active surveillance for problems patients encounter in the market place that result in allergic reactions and quickly acquire information on potential allergic reactions related to problems with manufacturing or labeling of food products.

## Center for Veterinary Medicine (CVM)

### EMERGING TECHNOLOGIES IN THE REVIEW OF NEW ANIMAL DRUG APPLICATIONS CVM #1

#### Current State

The advances in genomics and pharmacogenomics are rapid and applications to animal medicine are being embraced.

#### Scientific/Technical Limitation

There is a limitation in the ability to receive and analyze some types of genomic data effectively within CVM. Additional scientists with specialized expertise in areas such as genetically engineered animals, microarray gene expression data analysis, proteomics and genomic biomarkers are needed. We also need additional expertise in species varieties to appropriately review new therapies in many species (including minor species).

#### Scientific Areas

Proteomics, Genomics, Molecular biology, Toxicology, Biochemistry, Bioinformatics.

#### Examples of Strategic Opportunity

The field of genomics, genetics and specific animal models can further the knowledge of pathways and molecular mechanisms that underlie a variety of disorders, e.g., chronic inflammatory conditions, autoimmune disease, adverse drug interactions. This knowledge can enhance the drug evaluation process for safety and effectiveness of new animal drugs in a variety of species.

Animals can be genetically engineered for two overall purposes: to enhance their agronomic or production characteristics (e.g., being disease resistant or producing milk that spoils less readily or as sources of "biopharmed" products (producing human therapeutics in their milk or other antibodies to treat diseases in their blood). The potential to benefit public and animal health from these advances is significant.

## REVIEW OF HUMAN FOOD SAFETY ISSUES IN NEW ANIMAL DRUG APPLICATIONS—CVM #2

### Current State

Identifying the source of food-borne contamination (human, environmental or animal origin) through surveillance is an important step in preventing human infections

### Scientific/Technical Limitation

Scientific limitations at CVM in this area include:

- the need for additional expertise in analytical chemistry to verify the drug residue detection methods that sponsors submit in their new animal drug application for food producing species.
- the need to expand the surveillance conducted via the National Antimicrobial Resistance Monitoring System (NARMS).

### Scientific Areas

Bioinformatics, Chemistry, Immunology, Microbiology, Statistics, Toxicology.

### Examples of Strategic Opportunity

New validated methods would enable significant enhancement of CVM's understanding of and ability to monitoring the safety of food products from animals. Such methods would enable the Agency to respond to emerging drug residue problems when enforcement action is required.

Pulse Net, the national molecular sub-typing network for food-borne disease surveillance allows CVM to monitor emergence of multi-drug resistant food-borne pathogens. Data from the samples in Pulse Net provide a critical link with NARMS and together they can help lead to faster intervention and establishment of control measures during an outbreak of food-borne illness. As PulseNet identifies new, emerging pathogens over time, improved scientific capacity in these areas will allow us to identify and control them more rapidly and effectively.

## **MANUFACTURING AND CHEMISTRY REVIEW OF NEW ANIMAL DRUG APPLICATIONS—CVM #3**

### Current State

CVM is currently using the “traditional” model and does assays and validation on the completed product.

### Scientific/Technical Limitation

The value of innovative or novel manufacturing processes depends on the ability to validate and demonstrate robustness and reproducibility over time. The emergence of Process Analytical Technology (PAT) initiatives, Quality by Design (QBD), Design of Experiments (DOE) and nanotechnology necessitates the need for expertise in these areas. Guidance needs to be developed as new challenges arrive. Guidance documents need a clearer and more rapid path to completion and publication

### Scientific Areas

Biochemistry, Chemistry (Organic, Inorganic, Analytical), Molecular Biology, Nanoscience (Nanobiotechnology).

### Examples of Strategic Opportunity

Using multivariate analysis to maximize the efficiency of individual process steps, DOE will improve productivity and cost efficiency. Integrating risk analysis will help identify key risk factors that can compromise safety and quality of drug manufacturing. More and more we see the move toward various biologically derived materials (native tissue, transgenic sources, cell-derived products) which have more inherent variability compared to synthetics materials.

Greater capacity and knowledge in these new sciences will help CVM identify the factors that control the ability to make a product successfully (e.g., factors that impact product potency at various stages of the process).

## **SAFETY EVALUATION OF NEW ANIMAL ANTIMICROBIALS AND ANTIMICROBIAL RESISTANCE—CVM #4**

### Current State

To evaluate the potential impact of each new animal antimicrobial on the development of resistance in food-borne bacteria, it is necessary to identify relevant resistance genes present in animal production environments. Important data gaps exist that increase uncertainty in the pre-approval safety evaluation of new animal antimicrobials as it relates to antimicrobial resistance.

### Scientific/Technical Limitation

Improved scientific technological approaches are needed to generate data on the bacterial genetics of resistance and to provide biomarkers to help identify the animal origin of food-borne pathogens. While research using standard biochemical and genetic tools has been conducted to address these issues, they are labor intensive and often fail to provide definitive information.

### Scientific Areas

Biochemistry, Bioinformatics, Genetics, Microbiology, Molecular biology, Statistics

### Examples of Strategic Opportunity

High-throughput tools of molecular genetics, such as microarray and large scale DNA sequencing, are needed to provide a more comprehensive evaluation of the microbial ecosystems present in the intended use environments. This information will reduce uncertainty in the pre-approval process regarding the human food safety and environmental impact reviews, and help to predict shifts in antibiotic resistance that might occur in post-approval monitoring

A better understanding is needed to identify the antimicrobial use practices causing resistance in human clinical strains, it is necessary to identify the animal origin of a given human bacterial strain. This would allow regulatory authorities to provide science-based guidance on use practices impacting human health. New genetic and biochemical tools that would provide biomarkers indicating the likely animal origin of a given food-borne bacterial isolate are needed to address this data gap.

## **EVALUATION OF NOVEL ANIMAL FEED SUBSTANCES FOR SAFETY AND UTILITY— CVM #5**

### Current State

Genetically engineered plants are being developed to alter specific nutritional moieties (e.g., vitamins) but there is a lack of methods to readily identify the genetic modification that has been created.

### Scientific/Technical Limitation

For substances derived from biotechnology, there is no database or the ability to relate gene sequence to protein function and thus compositional changes and potential for toxin production. Also, there is a lack of methodologies to readily identify genetic modifications in plants and microorganisms and the resulting composition changes or potential for toxin production. Further, there is a lack of specialized, readily accessible scientific training in conduct of scientific review for these cutting edge biotechnologies. A greater understanding of metabolic differences between animal species and subpopulations within a species to identify the characteristics associated with optimal animal health and productivity is needed. There is a lack of biomarkers or genomic information to readily identify deficiencies in metabolic processes for some species and subpopulations of animals.

### Scientific Areas

Biochemistry, Bioinformatics, Genetics, Microbiology, Molecular biology.

### Examples of Strategic Opportunity

There is potential for a vast array of animal feed substances targeted at optimizing health and productivity of animals, and reducing waste products from animals by specifically changing the metabolism at the cellular level. These substances will likely be derived from biotech plants and microorganisms resulting from increased use of gene shuffling and site specific alterations in the genome. FDA needs better scientific knowledge of the animal metabolism and key pathways to optimize health and productivity, and reduced waste excretion to better accomplish its regulatory mission. Information is needed on intracellular signaling mechanisms. Robust models of the effects of genetic changes in plants and microorganisms will permit easier safety evaluations for compositional changes and toxin production.

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**POST MARKET SURVEILLANCE TO ENSURE THAT ANIMAL FEED PRODUCTS DERIVED FROM WASTE/CO-PRODUCTS FROM AGRICULTURAL/INDUSTRIAL PROCESSES IS SAFE FOR USE IN ANIMAL FEED—CVM #6**Current State

There is no adverse event reporting system for animal feeds and pet foods. Further, there is a lack of a database linking specific adverse effects with possible causes/toxins for specific animal species (dogs, cats, ruminants, swine, and poultry).

Scientific/Technical Limitation

A greater understanding is needed in the transfer of animal feed toxins into human food, e.g., milk and meat, and the how these toxins are metabolized in animals. There is a need for a database relating the transfer of animal feed toxins to human foods derived from animal products. The lack of these data reduces the capability of FDA to quickly follow up and effectively determine the cause of adverse events. There is also a lack of rapid methods for testing these contaminants in the various waste and co-products used in animal feeds (distiller's dried grains, glycerin, and other co-products from the biofuel industry as an example of an emerging technology).

Scientific Areas

Animal Science, Bioinformatics, Chemistry, Environmental Science, Microbiology, Toxicology, Veterinarian.

Examples of Strategic Opportunity

Rapidly expanding technologies and the need to reduce environmental waste increase the need to use the agricultural/industrial waste and co-products in the animal feed supply. For example, due to Presidential mandates to increase US biofuel production, this industry is competing for raw materials (ingredients for animal feed, e.g., corn and soybean) to make biofuel. The use of these unconventional materials to make biofuel will require close scrutiny to ensure the animal feeds produced with these co-products are safe for both animals and humans (meat, milk and eggs). The glut of these biofuel co-products will result in new uses in animal feeds (new uses in feeds for more animal species, and higher levels of these co-products will be included in animal feed). New rapid analytical methods are needed to ensure the safety of co-products in animal feed, and to close scientific gaps in knowledge of levels of toxins and the effects on the specific animal species and transfer of toxins and metabolites to human food products. FDA/CVM will need an IT infrastructure for an electronic adverse event reporting system for animal feeds.

**MAINTAIN A PUBLICLY AVAILABLE INVENTORY OF ALL MARKETED ANIMAL DRUGS TO ENSURE ADEQUATE INFORMATION IS AVAILABLE FOR REGULATORY ACTIVITY AND CUSTOMER SUPPORT—CVM #7**Current State

Currently, veterinary drug listing information is submitted in paper form and entry is done manually.

Scientific/Technical Limitation

Appropriate automation would allow CVM to focus on data analysis and quality control, rather than clerical data entry. There is a need for standardized medical dictionaries, data elements, and cross-reference with the electronic submission of adverse drug events; and the development of a standard electronic message.

Scientific Area

Bioinformatics, Pharmacy, Veterinarian.

Examples of Strategic Opportunity

There is a need for sharing drug listing and adverse event data with stakeholders, such as FDA field investigators and other Government agencies. The information gained through the listing of approved and unapproved products should be used to improve our detection of safety issues or product use. For example, if the adverse events in the safety section of the label in structured product labeling (SPL) were coded (via standardized medical dictionaries), reviewers could electronically compare the current label with the adverse events reported by industry to identify and enhance the detection of events that are not included in the currently approved label. The IT resources for automation of the drug listing should be identified. Ideally, labeling and its coding would be submitted electronically.

## ENSURING THE SAFETY AND EFFECTIVENESS OF MARKETED ANIMAL DRUGS, SPECIAL DIETARY FEEDS, AND OTHER VETERINARY MEDICAL PRODUCTS—CVM #8

### Current State

Today, most AE reports come to CVM in paper format using non standardized terms and vocabulary. We are implementing "PV Works," new software that is essential to successfully managing the ever increasing number of ADE reports annually submitted to the Center.

The statistical analysis of spontaneous adverse event reports is restricted because there is not a well defined control population. On the other hand, the treated population is large compared to randomized controlled studies with much smaller populations. Other limiting factors are the low reporting frequency, inconsistent terminology, and incomplete reports. These factors make it difficult to detect signals.

### Scientific/Technical Limitation

Limitations that hamper CVM's ability to move toward more useful and standardized AE reporting and analysis include:

- the absence of standardized medical dictionaries, standardized data elements for adverse drug event forms, electronic submission of adverse drug events and standard electronic messages are necessary.
- insufficient expertise in veterinary bioinformatics and statistics, to develop techniques for evaluating spontaneous ADEs, and improvements in the IT to receive electronic ADEs
- insufficient resource for training personnel in the proper use of PV Works, and for training in descriptive statistics.

There are also limitations in our capacity to appropriately communicate risk to the different CVM audiences, which stem from:

- insufficient resources to conduct awareness surveys to determine most useful labeling content (e.g., research to better understand how labeling design and layout could enhance public awareness of safety issues surrounding the use of veterinary products).
- insufficient expertise for evaluating promotional and advertisement activities, to optimize the public awareness of safety (i.e. encourage help seeking, disease awareness, *et cetera*).

### Scientific Areas

Bioinformatics, Epidemiology, Mathematics, Pharmacology, Pharmacy, Risk Assessor, Risk Communications, Toxicology, Veterinarian.

### Examples of Strategic Opportunity

Improved risk communication would help enhance public awareness of specific issues surrounding the usage of veterinary drug products and lead to avoidance or early intervention if adverse events developed. The development of a detailed, standardized

database that is searchable would generate highly informative ADEs.

## **EVALUATION AND PREVENTION OF CONTAMINATION OF ANIMAL FEED WITH HAZARDOUS MATERIALS FROM RENDERING FACILITIES—CVM #9**

### Current State

Currently a case-by-case analysis of any reported contaminated feeds with, for example, infectious agents, relies on what ever information is available. There are very few evidence-based standards to measure cross-contamination of rendered materials used in animal feeds.

### Scientific/Technical Limitation

There is a lack of evidence-based standards to prevent and measure the inadvertent cross contamination of animal diseases during the production of rendered material that is used in animal feed. The lack of national standards for methods and materials used to monitor the spread of infectious and sometimes communicable diseases during an animal disease outbreak can add to the further spread of a disease particulate when that contaminated material is unknowingly used in animal feed. Further, there is no ability to quickly, i.e., in a real time basis, and scientifically measure the success of cleanout procedures to prevent those hazards from entering animal feed at the rendering facility and to safely and efficiently go back into production of animal feed or animal feed ingredients.

### Scientific Areas

Animal Science, Chemistry Environmental Science, Epidemiology, Risk Assessor, Mathematics, Microbiology, Toxicology, Veterinarian.

### Examples of Strategic Opportunity

Animal Disease outbreaks including those with public health implications, zoonoses, will continue and/or possibly grow. Processing at rendering facilities will continue to be a critical stopgap in the disposition, disposal and recycling of animal waste and byproducts as sensitivities to environmental damage grows. Plans for greater control of infectious organisms and other hazards will be expected as prevention, response and recovery operations are established as the climate and potential for agroterrorism looms. Real time field rugged methods are needed for practical application, to support continuity of operations during regional emergencies.

## POST-MARKETING SURVEILLANCE AND DATA ANALYSIS—CVM #10

### Current State

FDA has implemented a number of surveillance tools to identify and monitor events of public health significance that may be associated with FDA approved products. These efforts range from large, cross-Agency data gathering tools (NARMS, FoodNet, PulseNet—all collaborations between FDA, CDC, and USDA focusing on food-borne diseases) to a proliferation of more Center-specific systems/databases (e.g., CVM's adverse drug event reporting and drug residues in meat and poultry systems).

### Scientific/Technical Limitation

There is insufficient scientific and IT activities in integrating the gathered data across programs.

For example, FDA samples imported seafood for pathogens and reports the results. If a limited number of these already-sampled pathogens could be further analyzed for antimicrobial resistance and PFGE patterns, we could obtain specific information on potential links between the identified pathogen and food-borne disease in the US, and more general information on trends in antimicrobial drug use in imported aquaculture, the possible role of imported seafood as a reservoir of antimicrobial resistant pathogens, and the potential association between pathogens on imported seafood and food-borne illness.

### Scientific Areas

Animal Science, Bioinformatics, Chemistry, Environmental Sciences, Epidemiology, Mathematics, Microbiology, Risk Assessor, Toxicology, Veterinarian.

### Examples of Strategic Opportunity

The performance goal of attaining shortened review times places a greater burden on surveillance systems to monitor trends than may impact the public health impact of these products. FDA needs to develop not just new electronic tools for "storing" data but better designed tools to maximize the use of that data. Even more important is to adopt a new approach to analyzing sets of data, one that involves identifying how shared data can be combined to address larger-scale issues that face the Center and FDA. Data analysis needs to rise above individual programs and encompass a broader spectrum of public health concerns and, importantly, this can be accomplished in cost-effective manner without requiring additional expansive (and expensive) data gathering.

## National Center for Toxicological Research (NCTR)

### ANALYTIC TOOLS AND EXPERTISE FOR REGULATORY SUPPORT DUE TO PACE OF CHANGE IN DISEASE PATTERNS AND TECHNOLOGY USE—NCTR #1

#### Current State

Issues like antibiotic resistance, rapid progress toward personalized medicine, and emerging technology use in FDA regulated products are creating gaps in regulatory review capacity that stem from limitations in availability of appropriate analytic tools, expertise, and scientific understanding.

#### Scientific/Technical Limitation

- Need for new molecular approaches and information (e.g., SNP/haplotype analysis, metabolomics, proteomics, genomics) to predict/identify human subpopulations at risk using noninvasive or minimally invasive sampling methods to define the metabolism, toxicity, efficacy, and/or susceptibility to regulated drugs, and other medical products, and microbes and contaminants in foods.
- Need to accelerate research for developing molecular biomarkers for diagnosis and treatment through, for example, incorporating pharmacogenomics into advanced personalized medicine
- Need to incorporate imaging approaches into preclinical assessments to improve translatable biomarkers of exposure and effect
- Need to develop statistical models and associated probabilistic methods that can accommodate vastly larger data volumes, biological modeling using panomics, and associated data characterization tools for uncertainty analysis for use in risk assessment of health endpoints
- Need for studies on risk associated with the use of nanomaterials in regulated consumer products
- The transformation of non-invasive technologies that will correlate to metabolic response of test species to clinical outcome and traditional markers of pathology.

#### Scientific Areas

Bioinformatics, Epidemiology, Genetics, Life Sciences, Mathematics, Molecular Biology, Nanotechnology, Panomics, Pharmacology, Toxicology.

#### Examples of Strategic Opportunity

- Improve the understanding of complex biological systems that will be essential in guiding the development of personalized nutrition and medicine
- Develop biomarkers and biometrical methods to aid in effective characterization of consumer risks and benefits

- Develop intervention strategies to reduce the frequency of multi-drug resistant microorganisms and key pathogens in the US food supply
- Develop methods to further understand and describe the ability of regulated products to cause adverse biological responses, for example: develop test methods for (and improve understanding of) biological interactions for generalizable properties of nanoscale materials; develop methods to monitor and predict interactions between human microbes and xenobiotic compounds or drugs.

## IMPLEMENTING PANOMICS IN REGULATORY REVIEW—NCTR #2

### Current State

As product sponsors increasingly move toward identifying subpopulations that will benefit from (or be at risk from) new products, FDA is receiving dramatically more and more types of information. Some data comes to us in the regulatory context, and other data through our Voluntary Genomic Data Submission program. With improved understanding and scientific validation, this data could speed and improve regulatory reviews. Today, however, this dramatic increase in panomic-based data and approaches is not integrated into regulatory review processes.

### Scientific/Technical Limitation

Critical need to:

- Develop and validate bioinformatics software that can support Agency review processes
- Learn how to manage and integrate data from the new technologies (e.g., *in silico* modeling, genomics, proteomics, and metabolomics) with traditional toxicological data
- Develop *in silico* approaches for predictive toxicology
- Maintain on-going access to state-of-the-art scientific equipment in the genomics, proteomics, and metabolomics fields
- Ensure that regulators have access to appropriate training, equipment, and software.

### Scientific Areas

Bioinformatics, Computational Chemistry, Panomics, Pharmacology, Statistics, Toxicology.

### Examples of Strategic Opportunity

Use computer technologies to predict adverse events from existing data and to predict the risk of exposure to biologically active products regulated by FDA.

## **Understanding How Individual Attributes Affect Human Response to Foods and Dietary Supplements—NCTR #3**

### Current State

Despite the increasing focus on nutrition and food safety, individuals may not have the information they need to choose a diet that is best for their unique genetic and metabolic attributes. The interactions between foods (including nutrients and dietary supplements) and individuals is largely unexplored.

### Scientific/Technical Limitation

There is a lack of understanding of how the unique attributes of individuals affect the safety of foods, food components, nutrients, and dietary supplements. FDA will need to explore novel scientific approaches, such as nutrigenomics and classification algorithms, to better our understanding.

### Scientific Areas

Bioinformatics, Genetics, Mathematics, Panomics, Pharmacology, Physiology, Toxicology.

### Examples of Strategic Opportunity

Characterize the risks and benefits of foods, food components, and dietary supplements using new approaches, such as nutrigenomics, to better understand how individual attributes affect response to foods, nutrients, and supplements.

## **RAPID DETECTION OF FOOD-BORNE PATHOGENS—NCTR #4**

### Current State

Current food-borne pathogen detection methods are limited in scope and have lengthy time requirements. Reasonably achievable improvements could decrease the number of consumers exposed.

### Scientific/Technical Limitation

Lack of quality high throughput techniques and/or multispecies detection methods for use in rapid detection of food-borne pathogens in FDA field labs.

### Scientific Areas

Chemistry, Microbiology, Toxicology.

### Examples of Strategic Opportunity

- Development of detection technologies and testing platforms that can be used at production, distribution, or retail facilities and make determination of food contamination rapidly, possibly within a matter of minutes versus days.
- Develop methods and recommend industry guidelines for evaluating the interactions of antimicrobial agents with human health.
- Develop intervention strategies to reduce the frequency of multi-drug resistant microorganisms and key pathogens in the US food supply.
- Develop, validate, share new technology, and improve commercial test kits for detection of food-borne pathogens, other select agents, and toxins in complex food matrices.

**SCIENTIFIC COMPUTING: INFORMATICS SUPPORT FOR MODERN PANOMICS AND TOXICOLOGY—NCTR #5**Current State

New panomic sciences (see #2 above, "Implementing Panomics in Regulatory Review") are generating terabytes of potentially useful information. Current FDA IT Infrastructure does not have the capacity to store and manipulate the vast datasets of information that can support the emerging technologies at the forefront.

Scientific/Technical Limitation

The lack of advanced scientific computing capacity is limiting the integration of panomic sciences, new toxicology approaches, and similar cutting edge science into regulatory processes.

Scientific Areas

Bioinformatics, Computational Chemistry, Panomics, Toxicology.

Examples of Strategic Opportunity

Improved infrastructure would further enhance scientific areas such as ArrayTrack™ and VXDS (voluntary 'cross-omics' data submission) and increase the ability of the Agency to translate the e-submission concept into practice. Also needed are bioinformatic modules to allow seamless electronic data submission to FDA including new 'omics' endpoints coupled with preclinical and clinical datasets.

**Table 1- Areas of Scientific Expertise Needed at FDA**

Major Scientific Expertise Type	Scientific Expertise Category	Specific Scientific Expertise	FDA Center Needs	Major Application to Regulation
<b>Life Sciences</b>				
	Animal Science	Physiology, Genetics, Nutrition, Production management, Toxicology, Cell culture	CBER CFSAN CVM	<ul style="list-style-type: none"> <li>▪ Animal product safety and efficacy</li> <li>▪ Animal nutrition</li> <li>▪ Alternatives to animal testing</li> <li>▪ BSL3 animal testing with select agents</li> <li>▪ Animal models disease modeling</li> </ul>
	Cell Biology	Cell signaling; Tumorigenesis; Apoptosis, Cell Culture	CBER CDRH CDER CFSAN CVM	<ul style="list-style-type: none"> <li>▪ In vitro safety assays</li> <li>▪ In vitro bioequivalence assessments</li> <li>▪ In vitro transport, distribution and toxicity, e.g., hepatotoxicity</li> <li>▪ Alternatives to animal testing</li> <li>▪ Cell therapy</li> <li>▪ Blood cell viability and storage</li> <li>▪ Cell substrates for biologics manufacturing</li> <li>▪ Hematopoietic stem cell development</li> <li>▪ Neurological product safety and efficacy</li> </ul>
	Developmental	Developmental immunology, Neurobiology, Nutrition	CBER CDER CFSAN CVM NCTR	<ul style="list-style-type: none"> <li>▪ Safety and efficacy of drugs and biologics various stages of development (e.g., fetus, infant, children, adult, aged)</li> <li>▪ Safety of food additives, and nutritional and dietary supplements</li> <li>▪ Food and human development</li> <li>▪ Alternatives to animal testing</li> </ul>
	Environmental Science		CBER CDER CDRH CFSAN CVM	<ul style="list-style-type: none"> <li>▪ Antibiotic resistance in microorganisms and gene product constructs</li> <li>▪ Environmental impact of products, e.g., contamination</li> </ul>

Major Scientific Expertise Type	Scientific Expertise Category	Specific Scientific Expertise	FDA Center Needs	Major Application to Regulation
	Genetics	Human genetics Molecular genetics Animal genetics	CBER CDER CDRH NCTR	<ul style="list-style-type: none"> <li>▪ Nutrition and development; mammalian gene mutation assay; toxicity of DNA damaging agents</li> <li>▪ Personalized medicine: responsiveness to products in animal models and in humans</li> <li>▪ Genetic biomarkers of product efficacy and safety</li> <li>▪ Transgenic animal models</li> <li>▪ Human genetics of rare diseases</li> <li>▪ Clinical response</li> <li>▪ Risk identification</li> <li>▪ Dose selection guidance</li> <li>▪ Susceptibility to adverse events and resistance to effects of drugs</li> <li>▪ Differential disease diagnosis</li> <li>▪ Polymorphic drug metabolism, transport and disease targets</li> <li>▪ Molecular epidemiology and emergence of food-borne pathogens</li> <li>▪ Biotech foods</li> </ul>
	Immunology	Humoral, Cellular, Innate, Allergy Molecular Immunology	CBER CDER CFSAN CVM NCTR	<ul style="list-style-type: none"> <li>▪ Vaccine efficacy</li> <li>▪ Blood efficacy and adverse events</li> <li>▪ Cell-tissue-gene efficacy</li> <li>▪ Allergy treatments</li> <li>▪ Allergenicity of food products, tissues, cell therapies, gene therapies, blood products, therapeutic proteins, monoclonal antibodies and other drugs</li> <li>▪ Loss of therapeutic potency due to immunogenicity</li> </ul>

Major Scientific Expertise Type	Scientific Expertise Category	Specific Scientific Expertise	FDA Center Needs	Major Application to Regulation
	Microbiology	Bacteriology, Virology, Mycology, Parasitology, Entomology, Transmissible Spongiform Encephalopathies, Parasitology	CBER CDER CDRH CFSAN CVM NCTR	<ul style="list-style-type: none"> <li>▪ Vaccine: Efficacy (attenuation) and Adverse Events (virulence)</li> <li>▪ Infectious gene vectors</li> <li>▪ Medical Product Sterility</li> <li>▪ Antimicrobial resistance</li> <li>▪ Human and animal food contamination</li> <li>▪ Biosecurity of foods and medical products</li> <li>▪ Select agent research</li> <li>▪ Epidemiology investigations of food and medical product contamination</li> <li>▪ Microbial forensics</li> <li>▪ Responses to public health threats from emerging pathogens</li> <li>▪ Evaluation of safety and efficacy of antimicrobial medical products</li> <li>▪ Organism virulence and attenuation mechanisms</li> <li>▪ Detection methods development; biomarkers</li> <li>▪ Microbial amplification techniques for identification</li> <li>▪ Virulence mechanisms</li> </ul>
	Molecular Biology	Antimicrobial Resistance; Drug Mechanisms; Molecular virology	CBER CDER CDRH CFSAN CVM NCTR	<ul style="list-style-type: none"> <li>▪ Transgenic animal models</li> <li>▪ Toxicogenomics</li> <li>▪ Models of carcinogenesis</li> <li>▪ Structure-function studies for viral vectors</li> <li>▪ DNA vaccines</li> <li>▪ Viral and bacterial genomic markers of vaccine attenuation</li> <li>▪ Standards for microarray methods and data</li> </ul>
	Neuroscience		CBER CDER CDRH CFSAN NCTR	<ul style="list-style-type: none"> <li>▪ Neuroactive drug safety and efficacy, e.g., anesthetics</li> <li>▪ Gene and cell therapy for neurological disease</li> <li>▪ Neurological imaging</li> <li>▪ Animal models of neurotoxicity</li> <li>▪ Vaccine neurotoxicity</li> </ul>

Major Scientific Expertise Type	Scientific Expertise Category	Specific Scientific Expertise	FDA Center Needs	Major Application to Regulation
	Pharmacology		CBER CDER CDRH CFSAN CVM NCTR	<ul style="list-style-type: none"> <li>▪ Pharmacovigilance</li> <li>▪ Pharmacokinetics</li> <li>▪ Pharmacodynamics</li> <li>▪ Drug-drug interactions</li> <li>▪ Mechanism of action of regulation and investigational products</li> <li>▪ Safety</li> </ul>
	Physiology		CBER CDER CDRH CVM NCTR	<ul style="list-style-type: none"> <li>▪ Comparative animal physiology</li> </ul>
	Panomics	Genomics (Gene expression microarray, bioinformatics)	CBER CDER CDRH CFSAN CVM NCTR	<ul style="list-style-type: none"> <li>▪ Clinical biomarkers of safety and efficacy</li> <li>▪ Biomarkers of vaccine, blood, cell-tissue-gene product quality</li> <li>▪ Biomarkers of cell substrates for vaccine and gene therapy manufacture</li> <li>▪ Biomarkers for preclinical efficacy and safety studies</li> <li>▪ Genetic variation of pathogens for nucleic acid-based blood donor screening test efficacy, food safety</li> <li>▪ Identification of food born pathogens</li> <li>▪ Molecular epidemiology</li> <li>▪ Microbial forensics</li> <li>▪ Molecular fingerprinting of microbial pathogens (PulseNet)</li> <li>▪ Comparative genomics</li> </ul>
		Metabolomics	NCTR	<ul style="list-style-type: none"> <li>▪ NMR-based metabolomics</li> <li>▪ Data quality and data analysis</li> </ul>

Major Scientific Expertise Type	Scientific Expertise Category	Specific Scientific Expertise	FDA Center Needs	Major Application to Regulation
		Proteomics (Mass Spectrometry)	CBER CDER CDRH CFSAN CVM NCTR	<ul style="list-style-type: none"> <li>▪ Clinical biomarkers of safety and efficacy</li> <li>▪ Biomarkers of vaccine, blood, cell-tissue-gene product quality, e.g., glycoprotein vaccines</li> <li>▪ Biomarkers of cell substrates for vaccine and gene therapy manufacture</li> <li>▪ Biomarkers for preclinical efficacy and safety studies</li> <li>▪ Methods development for allergens, GMO's and bacterial toxins</li> </ul>
	Toxicology	Carcinogenicity, antimicrobial resistance, tissue drug residues, Poisons	CBER CDER CDRH CFSAN CVM NCTR	<ul style="list-style-type: none"> <li>▪ Standard toxicology</li> <li>▪ Unique toxicology methods development needed for vaccine, blood &amp; blood product, Cell-Tissue-Gene therapy F</li> <li>▪ In vitro/in vivo safety assessments</li> <li>▪ Human and animal food safety</li> <li>▪ Phototoxicology</li> <li>▪ Reproductive toxicology</li> <li>▪ Carcinogenicity</li> <li>▪ Developmental toxicology</li> <li>▪ Genetic toxicology</li> <li>▪ Immunotoxicology</li> <li>▪ Alternatives to animal testing</li> <li>▪ Comparative toxicology</li> <li>▪ Microbial-chemical interactions</li> <li>▪ Alternatives to animal testing</li> </ul>

Major Scientific Expertise Type	Scientific Expertise Category	Specific Scientific Expertise	FDA Center Needs	Major Application to Regulation
<b>Nanosciences</b>				
	Nanobiology Nanobiotechnology Nanotechnology		CBER CDER CDRH CFSAN CVM NCTR	<ul style="list-style-type: none"> <li>▪ Using nanotechnology methods for medical product/food evaluation</li> <li>▪ Developing appropriate evaluation pathways for novel nanobiology products:                             <ul style="list-style-type: none"> <li>• Safety/toxicology (e.g., skin absorption)</li> <li>• OSHA issues</li> <li>• Assessment of processing and compositional variables</li> <li>• Quality testing</li> <li>• Physicochemical and pharmacokinetic evaluation</li> <li>• Chemical imaging and Process Analytical Technologies for rapid assessment</li> </ul> </li> </ul>
<b>Physical Sciences</b>				
				<ul style="list-style-type: none"> <li>▪ Regulatory analysis of medical products, including drugs, devices and biologicals, and foods</li> <li>▪ Analysis of adverse event reports, device failures, product quality</li> <li>▪ Mechanistic understanding of device performance, standards, test methods and forensic analysis</li> </ul>
	Chemistry	Organic	CBER CDER CVM NCTR	<ul style="list-style-type: none"> <li>▪ Product quality and purity</li> <li>▪ Blood safety (e.g., label adhesive technology; hemoglobin based oxygen carrier preclinical testing)</li> </ul>
		Inorganic	CBER CDER CDRH CVM NCTR	<ul style="list-style-type: none"> <li>▪ Product quality and purity</li> </ul>

Major Scientific Expertise Type	Scientific Expertise Category	Specific Scientific Expertise	FDA Center Needs	Major Application to Regulation
		Analytical	CBER CDER CDRH CFSAN CVM NCTR ORA	<ul style="list-style-type: none"> <li>▪ Human and animal drug and vaccine, blood, cell-tissue-gene, food quality and purity</li> <li>▪ Forensic investigations of contamination and counterfeiting</li> <li>▪ Medicated animal feeds and tissue residue test methods development</li> <li>▪ Foods and cosmetics analysis: chemical contaminants, food additives, pesticides, natural toxins, dietary supplements, colors, cosmetics</li> <li>▪ Color analysis and certification, standards</li> <li>▪ Food ingredient standard setting</li> </ul>
		Biochemistry	CBER CDER CDRH CFSAN CVM NCTR	<ul style="list-style-type: none"> <li>▪ Product quality and purity</li> <li>▪ Assays for bioterror and emerging infectious agents in medical products and food</li> <li>▪ Color Certification</li> <li>▪ rDNA technology</li> </ul>
		Physical	CBER CDER CFSAN CVM NCTR	<ul style="list-style-type: none"> <li>▪ Food product testing: decomposition, radiation, explosives</li> <li>▪ Medical product quality, identity and purity</li> <li>▪ Special techniques for foods analysis, e.g., ESR and neutron activation</li> <li>▪ Spectroscopy and chemometrics for quality assessment</li> </ul>
		Polymer	CBER CDRH	<ul style="list-style-type: none"> <li>▪ Vaccine and gene vector delivery systems and adjuvants</li> </ul>
	Physics			
		Biophysics	CDRH CBER	
		Atomic, Molecular, Optical, Chemical, Condensed Matter, Nuclear, Particle, Theoretical	CDRH	

Major Scientific Expertise Type	Scientific Expertise Category	Specific Scientific Expertise	FDA Center Needs	Major Application to Regulation
<b>Quantitative Sciences</b>				
	Mathematics	Statistics, Risk Analysis, Risk Assessment, Risk Management, Clinical Trial Design; Biostatistics, Pharmacometrics, Modeling and simulation	CBER CDER CDRH CFSAN CVM NCTR	<ul style="list-style-type: none"> <li>▪ Clinical trial design</li> <li>▪ Statistical analysis of pre-market drug applications for safety and efficacy</li> <li>▪ Methods for analysis of carcinogenesis, mutagenesis, toxicology data</li> <li>▪ Genomic signatures for high-dimensional data</li> <li>▪ Benefit/risk classification models for risk assessment</li> <li>▪ Toxicity prediction models</li> <li>▪ Risk based inspection paradigms</li> <li>▪ Process Analysis and modeling</li> </ul>
	Epidemiology	Pharmoepidemiology, Bioepidemiology, Pharmacovigilance	CBER CDER CDRH CFSAN CVM NCTR	<ul style="list-style-type: none"> <li>▪ Post-marketing studies for vaccines</li> <li>▪ Surveillance for vaccine, blood, cell-tissue-gene adverse events and product contamination</li> <li>▪ Post-market active and passive surveillance for adverse events</li> </ul>

Major Scientific Expertise Type	Scientific Expertise Category	Specific Scientific Expertise	FDA Center Needs	Major Application to Regulation
<b>Computing Sciences</b>				
	Computer Science, Bioinformatics	Medical terminology, clinical studies, statistics, data management, data mining, panomics technology	CBER CDER CDRH CFSAN CVM NCTR	<ul style="list-style-type: none"> <li>▪ Product quality</li> <li>▪ Adverse event surveillance</li> <li>▪ Biomarkers of disease and product toxicity</li> <li>▪ Data quality and data analysis challenges of the 'omics'</li> <li>▪ Human, animal and microbial genome databases and search methods</li> <li>▪ Standards development</li> <li>▪ Modeling and simulation</li> <li>▪ New Drug Application patient data</li> <li>▪ Pharmacogenetic/Pharmacogenomic data</li> <li>▪ Microbial forensics</li> <li>▪ Molecular epidemiology</li> <li>▪ Comparative genomics</li> <li>▪ Biomarkers and molecular signatures</li> </ul>
	Computers as management and communication tools	Web-based management and communications, scientific equipment support	CBER CDER CDRH CFSAN CVM NCTR	<ul style="list-style-type: none"> <li>▪ Research Program reporting and management</li> <li>▪ FDA Publication Databases</li> <li>▪ Laboratory equipment support</li> <li>▪ Color certification system</li> </ul>

Major Scientific Expertise Type	Scientific Expertise Category	Specific Scientific Expertise	FDA Center Needs	Major Application to Regulation
Manufacturing Sciences			CBER CDER CVM ORA	<ul style="list-style-type: none"> <li>▪ Aseptic processing</li> <li>▪ Barrier isolation technology</li> <li>▪ Fermentation</li> <li>▪ Purification</li> <li>▪ Lyophilization</li> <li>▪ Quality control: Reference reagents, Standards, Product Release Testing, Assay Qualification</li> <li>▪ Unit Operations</li> <li>▪ Process Analytical Technologies</li> <li>▪ Crystallization (on-line and at-line)</li> <li>▪ Pharmaceutical dosage form assessment</li> <li>▪ Design space assignments</li> </ul>
Engineering Sciences				<ul style="list-style-type: none"> <li>▪ Regulatory analysis of medical devices, including design, development, evaluation and manufacturing</li> <li>▪ Analysis of adverse event reports, device failures, product quality</li> <li>▪ Mechanistic understanding of device performance, standards, test methods</li> <li>▪ Forensic analysis</li> </ul>
	Analytical Biomechanical, Electrical, Biomedical  Civil, Electronics, Environmental, Human Factors, Industrial		CDRH	
	Chemical		CDRH CDER	<ul style="list-style-type: none"> <li>▪ Review of product manufacturing data</li> <li>▪ Review of manufacturing plans, product quality, cGMPs</li> <li>▪ Process Analytical Technology</li> <li>▪ Quality by Design</li> </ul>

Major Scientific Expertise Type	Scientific Expertise Category	Specific Scientific Expertise	FDA Center Needs	Major Application to Regulation
	Bioengineering		CDRH CBER	<ul style="list-style-type: none"> <li>▪ Tissue Engineering, e.g., Cell/Tissue-Matrix interactions</li> <li>▪ Combination products</li> </ul>
	Mechanical		CDER CDRH CBER	<ul style="list-style-type: none"> <li>▪ Modeling of processes and methods</li> <li>▪ Quality assessment of drugs and biologics with devices (e.g., TDDS, inhalation, transfusion devices)</li> </ul>
	Manufacturing, Materials Science, Nuclear, Quality, Reliability		CDRH	
	Software		CBER CDRH	<ul style="list-style-type: none"> <li>▪ Blood devices, e.g., apheresis equipment</li> <li>▪ Bloodbanking</li> </ul>
	Systems		CDRH	
<b>Health Sciences</b>				
	Physician	Infectious diseases, anesthesiology, cardiology, radiology, oncology, surgery, hematology, endocrinology, pharmacology, psychiatry, neurology, geriatrics, pathology, dermatology, ophthalmology, internal medicine, rheumatology	CBER CDER CDRH CFSAN	<ul style="list-style-type: none"> <li>▪ Clinical Trial Design</li> <li>▪ Clinical Trial Review Science</li> <li>▪ Review of pre- and post-market safety and efficacy of medical products</li> <li>▪ Developing animal models of disease</li> <li>▪ Pathogenesis of human disease</li> <li>▪ Adverse event review</li> <li>▪ Human subject protection (IRB)</li> <li>▪ Labeling</li> <li>▪ Public Health</li> <li>▪ Public Health Policy</li> <li>▪ Cosmetics regulation, including color certification</li> <li>▪ Allergenicity of foods and cosmetics</li> <li>▪ Cardiac stents, circulatory system, cell therapies</li> <li>▪ Interventional radiology</li> <li>▪ Anesthesiology and respiratory therapy</li> </ul>

Major Scientific Expertise Type	Scientific Expertise Category	Specific Scientific Expertise	FDA Center Needs	Major Application to Regulation
	Dentist		CDRH	
	Veterinarian	Infectious diseases, anesthesiology, cardiology, radiology, oncology, surgery, hematology, endocrinology, pharmacology, psychiatry, neurology, geriatrics, animal behavior, pathology, ophthalmology, dermatology, aquaculture, obstetrics, ENT, orthopedic surgery, plastic surgery, gastroenterology, comparative medicine	CVM CFSAN CBER CDER	<ul style="list-style-type: none"> <li>▪ Animal product testing design and review</li> <li>▪ Clinical Trial Review</li> <li>▪ Adverse events review</li> <li>▪ Labeling</li> <li>▪ Contamination incidents</li> <li>▪ Zoonoses</li> <li>▪ Public Health</li> <li>▪ Public Health Policy</li> <li>▪ Developing animal models of disease</li> <li>▪ Pathogenesis of animal disease</li> <li>▪ Review pre-clinical pathology reports</li> <li>▪ Consulting on drug-organ toxicity</li> </ul>
		Lab Animal Medicine Small Animal Large Animal Primate	CBER, CDER, CVM NCTR	<ul style="list-style-type: none"> <li>▪ Animal facilities</li> </ul>
	Clinical Pharmacology		CDER CBER CVM	<ul style="list-style-type: none"> <li>▪ Toxicity studies</li> <li>▪ Dosing</li> <li>▪ Pharmacokinetics/Pharmacodynamics                             <ul style="list-style-type: none"> <li>• Modeling and simulation</li> <li>• Comparability</li> <li>• Immunogenicity of biologics</li> </ul> </li> <li>▪ Drug metabolism/transport</li> <li>▪ Drug interactions</li> <li>▪ Pharmacometrics</li> <li>▪ Mechanisms of action</li> <li>▪ Disease modeling</li> <li>▪ Pharmacogenetics/pharmacogenomics</li> </ul>
	Nursing		CDRH CFSAN	

Major Scientific Expertise Type	Scientific Expertise Category	Specific Scientific Expertise	FDA Center Needs	Major Application to Regulation
	Clinical Laboratory Scientists		CBER CVM CDRH	<ul style="list-style-type: none"> <li>▪ Clinical Chemistry</li> </ul>
	Medical Technologists		CBER	
<b>Food Science</b>				
		Nutrition-Human	CFSAN NCTR	<ul style="list-style-type: none"> <li>▪ Dietetics</li> <li>▪ Toxicity assessment</li> </ul>
		Nutrition-Animal	CVM	
		Food Compliance	CFSAN CVM	
		Horticulture	CFSAN	
<b>Social and Behavioral Sciences</b>				
	Decision Sciences Consumer Science Public Policy Economics		CDER CFSAN OC	<ul style="list-style-type: none"> <li>▪ Expert and “mental” models of how physicians make prescribing decisions regarding drug treatment for pregnant and nursing women</li> <li>▪ Consumer’s perceptions/attitudes of the risk of food safety, e.g., terrorism</li> <li>▪ Comprehension of drug labeling and advertising</li> </ul>
	Cognitive Psychology, Risk Perception and Communication		CBER CDER CDRH CFSAN OC	<ul style="list-style-type: none"> <li>▪ Perceptions of recall notices</li> <li>▪ Consumer awareness of relationships between dietary substances and health or risk of disease</li> <li>▪ Effectiveness of public health advisories (e.g., methylmercury and fish, drugs)</li> <li>▪ Effectiveness of labeling statements for communicating different risks (e.g., condom and drug-labeling statement comprehension)</li> <li>▪ Consumer awareness and perception of safety of vaccines, e.g., autism</li> <li>▪ Consumer awareness and perception of safety of blood and blood products, e.g., TSE</li> </ul>

Major Scientific Expertise Type	Scientific Expertise Category	Specific Scientific Expertise	FDA Center Needs	Major Application to Regulation
	Social Psychology, Human Factors (warning effectiveness), behavioral health, communications		CBER CDER CDRH CFSAN CVM OC	<ul style="list-style-type: none"> <li>▪ Usefulness of the brief summary in prescription drug advertisements directed to consumers (DTC)</li> <li>▪ Effectiveness of communication of risks vs. benefits in DTC broadcast advertisements</li> <li>▪ Effects on understanding of different presentations for communicating health claims on food labeling to consumers (e.g., carbohydrate claims, known vs. unknown substance-disease relationships, studies of specific claims food sponsors want to use)</li> <li>▪ Pregnant women’s infant feeding practices</li> <li>▪ Patients’ and health care providers’ perceptions and behaviors associated with DTC promotion of prescription drugs</li> <li>▪ Compliance of advertisements with regulatory requirements</li> <li>▪ Perceptions and use of FDA and other sources of information about newly identified risks of medical products</li> <li>▪ Consumers’ perceptions of food derived from animal clones</li> <li>▪ Usability studies of FDA, CDER, CBER web sites</li> <li>▪ Consumers’ perceptions of the impact of nicotine on the human body</li> <li>▪ Preferences for and comprehension of OTC drug labeling formats</li> <li>▪ Perceptions and use of prescription drug labeling</li> <li>▪ Preferences and understanding of nutrition drug formats</li> <li>▪ Effects of advertising and promotional labeling</li> <li>▪ Consumer behavior</li> </ul>
	Neurobehavioral Sciences, psychology		NCTR	<ul style="list-style-type: none"> <li>▪ Neurobehavioral outcomes of drug/chemical exposure</li> </ul>

Major Scientific Expertise Type	Scientific Expertise Category	Specific Scientific Expertise	FDA Center Needs	Major Application to Regulation
	Economics	Risk management, risk assessment, econometrics, cost-benefit analysis, agricultural economics	CBER CFSAN	<ul style="list-style-type: none"> <li>▪ Product shortages</li> <li>▪ Sole source products</li> <li>▪ Cost benefit analysis for FDA regulations and guidance</li> <li>▪ Economics of agricultural practices</li> </ul>
<b>Lawyer</b>				
		Intellectual Property	CBER CDRH	<ul style="list-style-type: none"> <li>▪ Patents, Material Transfer Agreements, Cooperative Research Agreements (CRADA)</li> </ul>
<b>Writer-Editor</b>				
			CBER CDRH	

**Table 2-Current Scientific Limitations Mapped to Core Regulatory Functions**

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #1 – Pre-Market Review</b>		
1.1 Review and Assess InVitro/Bench Data (this category applies to data received during stages prior to marketing application; for similar information submitted in marketing application see Activity 1.7)	CBER <ul style="list-style-type: none"> <li>▪ Predictive Biomarkers For Biologics Medical Products—CBER #1</li> <li>▪ New Approaches to Pre-Market Review of Gene Therapy Products—CBER #2</li> <li>▪ Risk Management In Evaluating Novel Approaches For Tissue Engineering—CBER #5</li> <li>▪ Development of Predictive Biomarkers And Animal Models For Vaccine Therapies—CBER #10</li> <li>▪ Statistical Approaches For Biologics Clinical Data Sets—CBER #11</li> </ul>	3
	CDRH <ul style="list-style-type: none"> <li>▪ Device Applications of Genomics—CDRH #7</li> <li>▪ Nanotechnology—CDRH #9</li> </ul>	25
	CDER <ul style="list-style-type: none"> <li>▪ Predictive Preclinical Safety Models—CDER #1</li> <li>▪ Integrating Genomics Into Regulatory Activities—CDER #2</li> <li>▪ Identification and Qualification of Biomarkers for Safety and Efficacy—CDER #6</li> <li>▪ Safety, Efficacy and Characterization of Complex Biologic Products—CDER #11</li> <li>▪ Bioequivalence Science—CDER #12</li> <li>▪ Manufacturing Science—CDER #13</li> </ul>	41
	CVM <ul style="list-style-type: none"> <li>▪ Emerging Technologies in the Review of New Animal Drug Applications—CVM #1</li> </ul>	69
	NCTR <ul style="list-style-type: none"> <li>▪ Implementing Panomics in Regulatory Review—NCTR #2</li> <li>▪ Scientific Computing: Informatics Support for Modern Panomics and Toxicology—NCTR #5</li> </ul>	80

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #1 – Pre-Market Review</b>		
a. Review and assess laboratory test data to determine adequacy of preclinical data to support human testing		
b. Research and analysis to develop and qualify disease or product biomarkers	CBER <ul style="list-style-type: none"> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products— CBER #6</li> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products— CBER #7</li> <li>▪ Pre-Market Review and Product Quality Testing of Vaccine Therapies— CBER #9</li> </ul>	3
	CDRH <ul style="list-style-type: none"> <li>▪ Innovative Clinical Trial Design—CDRH #4</li> <li>▪ Medical Imaging and Computer-aided Diagnosis—CDRH #13</li> </ul>	25
	CDER <ul style="list-style-type: none"> <li>▪ Predictive Animal Models for Testing Bioterrorism Countermeasures— CDER #5</li> </ul>	41
	CVM <ul style="list-style-type: none"> <li>▪ Safety Evaluation of New Animal Antimicrobials and Antimicrobial Resistance—CVM #4</li> </ul>	69
	NCTR <ul style="list-style-type: none"> <li>▪ Analytic Tools and Expertise for Regulatory Support Due to Pace of Change in Disease Patterns and Technology Use—NCTR #1</li> <li>▪ Understanding How Individual Attributes Affect Human Response to and Dietary Supplements—NCTR #3</li> </ul>	80
c. Develop or evaluate test methods	CBER <ul style="list-style-type: none"> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products— CBER #6</li> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products— CBER #7</li> <li>▪ Pre-Market Review and Product Quality Testing of Vaccine Therapies— CBER #9</li> </ul>	3

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #1 – Pre-Market Review</b>		
	CDRH <ul style="list-style-type: none"> <li>▪ Safety of Medical Products Containing Software—CDRH #1</li> <li>▪ Human Factors—CDRH #10</li> </ul>	25
	CDER <ul style="list-style-type: none"> <li>▪ Predictive Animal Models for Testing Bioterrorism Countermeasures—CDER #5</li> <li>▪ In Silico Modeling Tools—CDER #8</li> </ul>	41
	CVM <ul style="list-style-type: none"> <li>▪ Review of Human Food Safety Issues in New Animal Drug Applications—CVM #2</li> <li>▪ Safety Evaluation of New Animal Antimicrobials and Antimicrobial Resistance—CVM #4</li> </ul>	69
	NCTR <ul style="list-style-type: none"> <li>▪ Analytic Tools and Expertise for Regulatory Support Due to Pace of Change in Disease Patterns and Technology Use—NCTR #1</li> <li>▪ Understanding How Individual Attributes Affect Human Response to and Dietary Supplements—NCTR #3</li> </ul>	80
d. Good Laboratory Practices site inspections	NCTR <ul style="list-style-type: none"> <li>▪ Risk-Based Inspectional Models—CDER #9</li> </ul>	80
1.2 Review and Assess Animal and Toxicology Data (this category applies to data received during stages prior to marketing application; for similar information submitted in marketing application see Activity 1.7)	CBER <ul style="list-style-type: none"> <li>▪ Predictive Biomarkers For Biologics Medical Products—CBER #1</li> <li>▪ New Approaches to Pre-Market Review of Gene Therapy Products—CBER #2</li> <li>▪ Risk Management in Evaluating Novel Approaches for Tissue Engineering—CBER #5</li> <li>▪ Development of Predictive Biomarkers and Animal Models for Vaccine Therapies—CBER #10</li> <li>▪ Statistical Approaches for Biologics Clinical Data Sets—CBER #11</li> </ul>	3

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #1 – Pre-Market Review</b>		
	CDRH <ul style="list-style-type: none"> <li>▪ Innovative Clinical Trial Design—CDRH #4</li> <li>▪ Device Applications of Genomics—CDRH #7</li> <li>▪ Nanotechnology—CDRH #9</li> </ul>	25
	CDER <ul style="list-style-type: none"> <li>▪ Predictive Pre-clinical Safety Models—CDER #1</li> <li>▪ Safety, Efficacy and Characterization of Complex Biologic Products—CDER #11</li> </ul>	41
	NCTR <ul style="list-style-type: none"> <li>▪ Implementing Panomics in Regulatory Review—NCTR #2</li> <li>▪ Scientific Computing: Informatics Support for Modern Panomics and Toxicology—NCTR #5</li> </ul>	80
a. Review and assess animal pharmacology and toxicology data, to determine: adequacy of preclinical safety data to support human testing; safety assessment of infant formula, food additives and contact substances, new dietary ingredients, [color additives, GRAS food ingredients]	CVM <ul style="list-style-type: none"> <li>▪ Evaluation of Novel Animal Feed Substances for Safety and Utility—CVM #5</li> </ul>	69
b. Research and analysis to develop and qualify disease or product biomarkers	CBER <ul style="list-style-type: none"> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products—CBER #6</li> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products—CBER #7</li> <li>▪ Pre-Market Review and Product Quality Testing of Vaccine Therapies—CBER #9</li> </ul>	3
	CDRH <ul style="list-style-type: none"> <li>▪ Modeling Biological Processes—CDRH #5</li> </ul>	25

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #1 – Pre-Market Review</b>		
	CDER <ul style="list-style-type: none"> <li>▪ Integrating Genomics Into Regulatory Activities—CDER #2</li> <li>▪ Predictive Animal Models for Testing Bioterrorism Countermeasures—CDER #5</li> <li>▪ Identification and Qualification of Qualified Biomarkers for Safety and Efficacy—CDER #6</li> </ul>	41
	CVM <ul style="list-style-type: none"> <li>▪ Emerging Technologies in the Review of New Animal Drug Applications—CVM #1</li> </ul>	69
	NCTR <ul style="list-style-type: none"> <li>▪ Analytic Tools and Expertise for Regulatory Support Due to Pace of Change in Disease Patterns and Technology Use—NCTR #1</li> <li>▪ Understanding How Individual Attributes Affect Human Response to and Dietary Supplements—NCTR #3</li> </ul>	80
c. Develop or evaluate test methods	CBER <ul style="list-style-type: none"> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products—CBER #6</li> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products—CBER #7</li> <li>▪ Pre-Market Review and Product Quality Testing of Vaccine Therapies—CBER #9</li> </ul>	3
	CDRH <ul style="list-style-type: none"> <li>▪ Combination Products—CDRH #12</li> </ul>	25
	CDER <ul style="list-style-type: none"> <li>▪ Integrating Genomics Into Regulatory Activities—CDER #2</li> <li>▪ Predictive Animal Models for Testing Bioterrorism Countermeasures—CDER #5</li> <li>▪ Identification and Qualification of Biomarkers for Safety and Efficacy—CDER #6</li> <li>▪ In Silico Modeling Tools—CDER #8</li> </ul>	41

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #1 – Pre-Market Review</b>		
	CVM <ul style="list-style-type: none"> <li>▪ Review of Human Food Safety Issues in New Animal Drug Applications—CVM #2</li> </ul>	69
1.3 Review and Assess Data from Tests in Animal Models	CBER <ul style="list-style-type: none"> <li>▪ Development of Predictive Biomarkers and Animal Models for Vaccine Therapies—CBER #10</li> <li>▪ Statistical Approaches for Biologics Clinical Data Sets—CBER #11</li> </ul>	3
	CDRH <ul style="list-style-type: none"> <li>▪ Innovative Clinical Trial Design—CDRH #4</li> <li>▪ Device Applications of Genomics—CDRH #7</li> <li>▪ Nanotechnology—CDRH #9</li> </ul>	25
	CDER <ul style="list-style-type: none"> <li>▪ Predictive Pre-clinical Safety Models—CDER #1</li> <li>▪ Identification and Qualification of Biomarkers for Safety and Efficacy—CDER #6</li> <li>▪ Safety, Efficacy and Characterization of Complex Biologic Products—CDER #11</li> </ul>	41
	NCTR <ul style="list-style-type: none"> <li>▪ Implementing Panomics in Regulatory Review—NCTR #2</li> <li>▪ Scientific Computing: Informatics Support for Modern Panomics and Toxicology—NCTR #5</li> </ul>	80
a. Review/evaluate data in IND/IDE/510k submissions to determine whether preclinical efficacy data support the proposed clinical testing plan	CDER <ul style="list-style-type: none"> <li>▪ Integrating Genomics Into Regulatory Activities—CDER #2</li> </ul>	41
b. Review of data supporting efficacy for treatments of CT agents (Animal Efficacy rule)	CDER <ul style="list-style-type: none"> <li>▪ Integrating Genomics Into Regulatory Activities—CDER #2</li> <li>▪ Predictive Animal Models for Testing Bioterrorism Countermeasures—CDER #5</li> </ul>	41

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #1 – Pre-Market Review</b>		
c. Research and analysis to develop and qualify disease or product biomarkers	CDER <ul style="list-style-type: none"> <li>▪ Integrating Genomics Into Regulatory Activities—CDER #2</li> </ul>	41
	CVM <ul style="list-style-type: none"> <li>▪ Emerging Technologies in the Review of New Animal Drug Applications—CVM #1</li> </ul>	69
d. Develop or evaluate test methods and animal models	CBER <ul style="list-style-type: none"> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products—CBER #6</li> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products—CBER #7</li> <li>▪ Pre-Market Review and Product Quality Testing of Vaccine Therapies—CBER #9</li> </ul>	3
	CDRH <ul style="list-style-type: none"> <li>▪ Combination Products—CDRH #12</li> </ul>	25
	NCTR <ul style="list-style-type: none"> <li>▪ Analytic Tools and Expertise for Regulatory Support Due to Pace of Change in Disease Patterns and Technology Use—NCTR #1</li> <li>▪ Understanding How Individual Attributes Affect Human Response to and Dietary Supplements—NCTR #3</li> </ul>	80
1.4 Oversee Clinical Trials of Investigational Medical Products and Food Ingredients	CBER <ul style="list-style-type: none"> <li>▪ Development of Predictive Biomarkers and Animal Models for Vaccine Therapies—CBER #10</li> <li>▪ Statistical Approaches for Biologics Clinical Data Sets—CBER #11</li> <li>▪ Diagnostic Testing of Biologics Medical Products—CBER #12</li> </ul>	3
	CDRH <ul style="list-style-type: none"> <li>▪ Innovative Clinical Trial Design—CDRH #4</li> <li>▪ Modeling Biological Processes—CDRH #5</li> <li>▪ Device Applications of Genomics—CDRH #7</li> <li>▪ Nanotechnology—CDRH #9</li> </ul>	25

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #1 – Pre-Market Review</b>		
	CDER <ul style="list-style-type: none"> <li>▪ Safety, Efficacy and Characterization of Complex Biologic Products—CDER #11</li> </ul>	41
	CVM <ul style="list-style-type: none"> <li>▪ Safety Evaluation of New Animal Antimicrobials and Antimicrobial Resistance—CVM #4</li> </ul>	69
a. Review proposed protocols for: adequate safety, appropriate trial design and data analysis (including appropriate endpoints and safety biomarkers)	CDER <ul style="list-style-type: none"> <li>▪ Integrating Genomics Into Regulatory Activities—CDER #2</li> <li>▪ Innovative Clinical Trial Designs—CDER #4</li> <li>▪ Identification and Qualification of Biomarkers for Safety and Efficacy—CDER #6</li> <li>▪ Active Safety Surveillance—CDER #7</li> <li>▪ In Silico Modeling Tools—CDER #8</li> <li>▪ Better Tools for Pediatric Drug Development—CDER #10</li> </ul>	41
	CVM <ul style="list-style-type: none"> <li>▪ Emerging Technologies in the Review of New Animal Drug Applications—CVM #1</li> </ul>	69
b. IRB and clinical trial site inspections, monitoring trials to ensure patient protections (BiMo)	CDER <ul style="list-style-type: none"> <li>▪ Risk-Based Inspectional Models—CDER #9</li> </ul>	41
c. Receive, analyze and respond to complaints		

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #	
<b>Core Activity #1 – Pre-Market Review</b>			
1.5 Review Manufacturing and Product Quality for Investigational Studies (this category applies to data received during stages prior to marketing application; for similar information submitted in marketing application see Activity 1.7)	CBER <ul style="list-style-type: none"> <li>▪ PREDICTIVE BIOMARKERS FOR BIOLOGICS MEDICAL PRODUCTS—CBER #1</li> <li>▪ New Approaches to Pre-Market Review of Gene Therapy Products—CBER #2</li> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products—CBER #6</li> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products—CBER #7</li> <li>▪ Pre-Market Review and Product Quality Testing of Vaccine Therapies—CBER #9</li> <li>▪ Development of Predictive Biomarkers and Animal Models for Vaccine Therapies—CBER #10</li> <li>▪ Statistical Approaches for Biologics Clinical Data Sets—CBER #11</li> </ul>	<b>Error! Book mark not defined.</b>	
	CDRH <ul style="list-style-type: none"> <li>▪ Device Applications of Genomics—CDRH #7</li> <li>▪ Nanotechnology—CDRH #9</li> </ul>		25
	CDER <ul style="list-style-type: none"> <li>▪ Safety, Efficacy and Characterization of Complex Biologic Products—CDER #11</li> <li>▪ Manufacturing Science—CDER #13</li> </ul>		41
	CFSAN <ul style="list-style-type: none"> <li>▪ Food Production Sciences: Risk Mitigation at the Source—CFSAN #1</li> </ul>		57
	CVM <ul style="list-style-type: none"> <li>▪ Evaluation of Novel Animal Feed Substances for Safety and Utility—CVM #5</li> </ul>		3
	NCTR <ul style="list-style-type: none"> <li>▪ Scientific Computing: Informatics Support for Modern Panomics and Toxicology—NCTR #5</li> </ul>		80

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #1 – Pre-Market Review</b>		
a. Product characterization review (e.g., review identity, potency, sterility, materials compatibility, prototype and materials review)	CBER <ul style="list-style-type: none"> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products— CBER #6</li> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products— CBER #7</li> <li>▪ Pre-Market Review and Product Quality Testing of Vaccine Therapies— CBER #9</li> </ul>	3
	CVM <ul style="list-style-type: none"> <li>▪ Manufacturing and Chemistry Review of New Animal Drug Applications—CVM #3</li> </ul>	69
b. Product manufacturing processes and stability review (includes drug synthesis, drug and biologic impurities assessment, quality control methods, Good Manufacturing Practices inspection)	CDER <ul style="list-style-type: none"> <li>▪ Risk-Based Inspectional Models—CDER #9</li> </ul>	41
	CVM <ul style="list-style-type: none"> <li>▪ Manufacturing and Chemistry Review of New Animal Drug Applications—CVM #3</li> </ul>	69
c. Develop or evaluate test methods	CBER <ul style="list-style-type: none"> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products— CBER #6</li> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products— CBER #7</li> <li>▪ Pre-Market Review and Product Quality Testing of Vaccine Therapies— CBER #9</li> </ul>	3
	CVM <ul style="list-style-type: none"> <li>▪ Review of Human Food Safety Issues in New Animal Drug Applications—CVM #2</li> </ul>	69
1.6 Review, Assess, and Respond to Requests for “Humanitarian” Uses of Investigational Products		

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #1 – Pre-Market Review</b>		
1.7 Review Marketing Applications and/or Product Notifications (including re-submitted products, efficacy supplements, transgenic/genetically modified animals)	CDRH <ul style="list-style-type: none"> <li>▪ Device Applications of Genomics—CDRH #7</li> <li>▪ Nanotechnology—CDRH #9</li> <li>▪ Closed Loop Systems—CDRH #11</li> <li>▪ Combination Products—CDRH #12</li> </ul>	25
	CDER <ul style="list-style-type: none"> <li>▪ Better Tools for Pediatric Drug Development—CDER #10</li> </ul>	41
	CFSAN <ul style="list-style-type: none"> <li>▪ Food Production Sciences: Risk Mitigation at the Source—CFSAN #1</li> <li>▪ Regulatory Programs to Implement the Food Allergen Labeling and Consumer Protection Act (FALCPA) and Advancing Effective Interventions—CFSAN #3</li> </ul>	57
	CVM <ul style="list-style-type: none"> <li>▪ Evaluation of Novel Animal Feed Substances for Safety and Utility—CVM #5</li> </ul>	69
	NCTR <ul style="list-style-type: none"> <li>▪ Implementing Panomics in Regulatory Review—NCTR #2</li> <li>▪ Scientific Computing: Informatics Support for Modern Panomics and Toxicology—NCTR #5</li> </ul>	80

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #1 – Pre-Market Review</b>		
<p>a. Review of clinical safety and/or efficacy results (for human medical products, infant formula, food and color additive, GRAS food ingredients, feed additives, new dietary ingredients, review of food health claims)</p> <ul style="list-style-type: none"> <li>i. Statistical review</li> <li>ii. Clinical review (including adverse events)</li> <li>iii. Clinical pharmacology review</li> <li>iv. Pediatric assessment for development, if under Pediatric Research Equity Act</li> <li>v. Review of biologic equivalence (generics)</li> <li>vi. Literature review (e.g., Generally Recognized As Safe notifications)</li> </ul>	<p>CDER</p> <ul style="list-style-type: none"> <li>▪ Integrating Genomics Into Regulatory Activities—CDER #2</li> <li>▪ Innovative Clinical Trial Designs—CDER #4</li> <li>▪ Identification and Qualification of Biomarkers for Safety and Efficacy—CDER #6</li> <li>▪ Active Safety Surveillance—CDER #7</li> <li>▪ In Silico Modeling Tools—CDER #8</li> <li>▪ Safety, Efficacy and Characterization of Complex Biologic Products—CDER #11</li> <li>▪ Bioequivalence Science—CDER #12</li> </ul>	41
	<p>CVM</p> <ul style="list-style-type: none"> <li>▪ Emerging Technologies in the Review of New Animal Drug Applications—CVM #1</li> </ul>	69
<p>b. Review non-clinical data supporting marketing application.</p> <ul style="list-style-type: none"> <li>i. Human food safety (review/validate sponsor's NADA in vitro test method for drug residues in animal tissues and milk, safety review for food and color additives, review test methods)</li> <li>ii. Review of any special toxicologic studies, e.g., reproductive toxicology or carcinogenicity</li> <li>iii. Animal Efficacy review, where applicable; review food nutrient content claims</li> <li>v. Review of device performance</li> <li>vi. Review of chemical equivalence (generics)</li> </ul>	<p>CDRH</p> <ul style="list-style-type: none"> <li>▪ Safety of Medical Products Containing Software—CDRH #1</li> <li>▪ Reuse of Single Use Devices (SUDs) CDRH #2</li> </ul>	25
	<p>CDER</p> <ul style="list-style-type: none"> <li>▪ Predictive Pre-clinical Safety Models—CDER #1</li> <li>▪ Integrating Genomics Into Regulatory Activities—CDER #2</li> <li>▪ Predictive Animal Models for Testing Bioterrorism Countermeasures—CDER #5</li> <li>▪ Identification and Qualification Biomarkers for Safety and Efficacy—CDER #6</li> <li>▪ Safety, Efficacy and Characterization of Complex Biologic Products—CDER #11</li> <li>▪ Bioequivalence Science—CDER #12</li> </ul>	41

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #1 – Pre-Market Review</b>		
	CVM <ul style="list-style-type: none"> <li>▪ Emerging Technologies in the Review of New Animal Drug Applications—CVM #1</li> <li>▪ Manufacturing and Chemistry Review of New Animal Drug Applications—CVM #3</li> <li>▪ Safety Evaluation of New Animal Antimicrobials and Antimicrobial Resistance—CVM #4</li> </ul>	69
c. Review of the effect of products on the environment	CBER <ul style="list-style-type: none"> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products—CBER #6</li> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products—CBER #7</li> <li>▪ Pre-Market Review and Product Quality Testing of Vaccine Therapies—CBER #9</li> </ul>	3
	CVM <ul style="list-style-type: none"> <li>▪ Emerging Technologies in the Review of New Animal Drug Applications—CVM #1</li> <li>▪ Manufacturing and Chemistry Review of New Animal Drug Applications—CVM #3</li> </ul>	69
	NCTR <ul style="list-style-type: none"> <li>▪ Analytic Tools and Expertise for Regulatory Support Due to Pace of Change in Disease Patterns and Technology Use—NCTR #1</li> <li>▪ Understanding How Individual Attributes Affect Human Response to and Dietary Supplements—NCTR #3</li> </ul>	80
d. Review variance and exemption requests for radiation emitting products (that are not otherwise medical devices)	CBER <ul style="list-style-type: none"> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products—CBER #6</li> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products—CBER #7</li> <li>▪ Pre-Market Review and Product Quality Testing of Vaccine Therapies—CBER #9</li> </ul>	3



Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #1 – Pre-Market Review</b>		
g. Label review: risk and benefit communication, instructions for use	CDER <ul style="list-style-type: none"> <li>▪ Risk Communication—CDRH #6</li> <li>▪ Risk Communications—CDER #14</li> </ul>	41
	CVM <ul style="list-style-type: none"> <li>▪ Safety Evaluation of New Animal Antimicrobials and Antimicrobial Resistance—CVM #4</li> </ul>	69
	NCTR <ul style="list-style-type: none"> <li>▪ Analytic Tools and Expertise for Regulatory Support Due to Pace of Change in Disease Patterns and Technology Use—NCTR #1</li> <li>▪ Understanding How Individual Attributes Affect Human Response to and Dietary Supplements—NCTR #3</li> </ul>	80
h. Review promotional material	CDER <ul style="list-style-type: none"> <li>▪ Risk Communication—CDRH #6</li> <li>▪ Risk Communications—CDER #14</li> </ul>	41

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #1 – Pre-Market Review</b>		
1.8 Consultative Meetings with Sponsors	<p>CDER</p> <ul style="list-style-type: none"> <li>▪ Predictive Pre-clinical Safety Models—CDER #1</li> <li>▪ Integrating Genomics Into Regulatory Activities—CDER #2</li> <li>▪ Innovative Clinical Trial Designs—CDER #4</li> <li>▪ Predictive Animal Models for Testing Bioterrorism Countermeasures—CDER #5</li> <li>▪ Identification and Qualification of Biomarkers for Safety and Efficacy—CDER #6</li> <li>▪ Active Safety Surveillance—CDER #7</li> <li>▪ In Silico Modeling Tools—CDER #8</li> <li>▪ Risk-Based Inspectional Models—CDER #9</li> <li>▪ Better Tools for Pediatric Drug Development—CDER #10</li> <li>▪ Safety, Efficacy and Characterization of Complex Biologic Products—CDER #11</li> <li>▪ Bioequivalence Science—CDER #12</li> <li>▪ Manufacturing Science—CDER #13</li> <li>▪ Risk Communications—CDER #14</li> </ul>	41
	<p>CVM</p> <ul style="list-style-type: none"> <li>▪ Emerging Technologies in the Review of New Animal Drug Applications—CVM #1</li> <li>▪ Review of Human Food Safety Issues in New Animal Drug Applications—CVM #2</li> <li>▪ Evaluation of Novel Animal Feed Substances for Safety and Utility—CVM #5</li> </ul>	69
	<p>NCTR</p> <ul style="list-style-type: none"> <li>▪ Implementing Panomics in Regulatory Review—NCTR #2</li> <li>▪ Understanding How Individual Attributes Affect Human Response to and Dietary Supplements—NCTR #3</li> </ul>	80

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #1 – Pre-Market Review</b>		
1.9 Standards/Guidance Development	CBER <ul style="list-style-type: none"> <li>▪ Predictive Biomarkers for Biologics Medical Products—CBER #1</li> <li>▪ New Approaches to Pre-Market Review of Gene Therapy Products—CBER #2</li> <li>▪ Risk Management in Evaluating Novel Approaches for Tissue Engineering—CBER #5</li> <li>▪ Development of Predictive Biomarkers and Animal Models for Vaccine Therapies—CBER #10</li> <li>▪ Statistical Approaches for Biologics Clinical Data Sets—CBER #11</li> <li>▪ Diagnostic Testing of Biologics Medical Products—CBER #12</li> </ul>	3
	CDRH <ul style="list-style-type: none"> <li>▪ Safety of Medical Products Containing Software—CDRH #1</li> <li>▪ Reuse of Single Use Devices—CDRH #2</li> <li>▪ Device Applications of Genomics—CDRH #7</li> <li>▪ Nanotechnology—CDRH #9</li> <li>▪ Human Factors—CDRH #10</li> <li>▪ Closed Loop Systems—CDRH #11</li> <li>▪ Combination Products—CDRH #12</li> <li>▪ Medical Imaging and Computer-aided Diagnosis—CDRH #13</li> <li>▪ Risk Communications—CDER #14</li> </ul>	25

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #1 – Pre-Market Review</b>		
	<p>CDER</p> <ul style="list-style-type: none"> <li>▪ Predictive Pre-clinical Safety Models—CDER #1</li> <li>▪ Innovative Clinical Trial Designs—CDER #4</li> <li>▪ Predictive Animal Models for Testing Bioterrorism Countermeasures—CDER #5</li> <li>▪ Identification and Qualification of Biomarkers for Safety and Efficacy—CDER #6</li> <li>▪ Active Safety Surveillance—CDER #7</li> <li>▪ In Silico Modeling Tools—CDER #8</li> <li>▪ Risk-Based Inspectional Models—CDER #9</li> <li>▪ Better Tools for Pediatric Drug Development—CDER #10</li> <li>▪ Safety, Efficacy and Characterization of Complex Biologic Products—CDER #11</li> <li>▪ Bioequivalence Science—CDER #12</li> <li>▪ Manufacturing Science—CDER #13</li> <li>▪ Risk Communication—CDRH #6</li> </ul> <p>CFSAN</p> <ul style="list-style-type: none"> <li>▪ Food Production Sciences: Risk Mitigation at the Source—CFSAN #1</li> </ul> <p>NCTR</p> <ul style="list-style-type: none"> <li>▪ Implementing Panomics in Regulatory Review—NCTR #2</li> <li>▪ Scientific Computing: Informatics Support for Modern Panomics and Toxicology—NCTR #5</li> </ul>	<p>41</p> <p>57</p> <p>80</p>
<p>a. Scientific Standards—development of technical and scientific standards, domestic and international harmonization of such standards (e.g., for bench and preclinical assessment; for product development such as product specific clinical trial designs, statistical standards; for product manufacturing and quality)</p>	<p>CDER</p> <ul style="list-style-type: none"> <li>▪ Integrating Genomics Into Regulatory Activities—CDER #2</li> </ul>	<p>41</p>

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #1 – Pre-Market Review</b>		
	CVM <ul style="list-style-type: none"> <li>▪ Emerging Technologies in the Review of New Animal Drug Applications—CVM #1</li> <li>▪ Manufacturing and Chemistry Review of New Animal Drug Applications—CVM #3</li> <li>▪ Evaluation of Novel Animal Feed Substances for Safety and Utility—CVM #5</li> </ul>	69
b. Data Standards—development of data standards (e.g., electronic standards for submissions, ingredient terminologies, labels), domestic and international development and harmonization of such standards	CVM <ul style="list-style-type: none"> <li>▪ Review of Human Food Safety Issues in New Animal Drug Applications—CVM # 2</li> </ul>	69

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #2—Marketed Product Adverse Event Surveillance and Efficacy/Safety Assessment</b>		
2.1 Receive and Analyze Reports of Adverse Events, Accidental Radiation Occurrences, Product Failures	CBER <ul style="list-style-type: none"> <li>▪ Post-Market Surveillance of Blood Products—CBER #14</li> <li>▪ Post-Market Surveillance and Quality Assurance of Biologic Medical Products—CBER #1</li> </ul>	3
	CDRH <ul style="list-style-type: none"> <li>▪ Adverse Event Detection, Data, and Analysis—CDRH #8</li> </ul>	25
	CDER <ul style="list-style-type: none"> <li>▪ Active Safety Surveillance—CDER #7</li> </ul>	41
	CFSAN <ul style="list-style-type: none"> <li>▪ Adverse Event Reporting and Analysis—CFSAN #7</li> <li>▪ Regulatory Programs to Implement the Food Allergen Labeling and Consumer Protection Act (FALCPA) and Advancing Effective Interventions—CFSAN #3</li> </ul>	57
	CVM <ul style="list-style-type: none"> <li>▪ Safety Evaluation of New Animal Antimicrobials and Antimicrobial Resistance—CVM #4</li> <li>▪ Post Market Surveillance to Ensure that Animal Feed Products Derived from Waste/Co-products from Agricultural/Industrial Processes is Safe for Use in Animal Feed—CVM #6</li> <li>▪ Maintain a Publicly Available Inventory of All Marketed Animal Drugs to Ensure Adequate Information is Available for Regulatory Activity and Customer Support—CVM #7</li> <li>▪ Ensuring the Safety and Effectiveness of Marketed Animal Drugs, Special Dietary Feeds, and other Veterinary Medical Products—CVM #8</li> <li>▪ Post-Marketing Surveillance and Data Analysis—CVM #10</li> </ul>	69
	NCTR <ul style="list-style-type: none"> <li>▪ Implementing Panomics in Regulatory Review—NCTR #2</li> </ul>	80

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #2—Marketed Product Adverse Event Surveillance and Efficacy/Safety Assessment</b>		
a. Establish and manage procedures to receive and assess reports and complaints	CDRH <ul style="list-style-type: none"> <li>▪ Modeling Biological Processes—CDRH #5</li> </ul>	25
b. Establish links to external entities (e.g., other public health agencies) to monitor or evaluate reports (e.g., food contamination outbreaks, infectious disease outbreaks, tissue drug residues.)	CDRH <ul style="list-style-type: none"> <li>▪ Risk Communication—CDRH #6</li> </ul>	25
	CVM <ul style="list-style-type: none"> <li>▪ Review of Human Food Safety Issues in New Animal Drug Applications—CVM #2</li> </ul>	69
c. Design/undertake studies of data received (e.g., studies required by Best Pharmaceuticals for Children Act)	CDER <ul style="list-style-type: none"> <li>▪ Integrating Genomics Into Regulatory Activities—CDER #2</li> <li>▪ Identification and Qualification of Biomarkers for Safety and Efficacy—CDER #6</li> <li>▪ Better Tools for Pediatric Drug Development—CDER #10</li> </ul>	41
2.2 Active Surveillance / Signal Detection Activities	CBER <ul style="list-style-type: none"> <li>▪ Post-Market Surveillance of Blood Products—CBER #14</li> <li>▪ Post-Market Surveillance and Quality Assurance of Biologic Medical Products—CBER #15</li> </ul>	3
	CDRH <ul style="list-style-type: none"> <li>▪ Adverse Event Detection, Data, and Analysis—CDRH #8</li> </ul>	25
	CFSAN <ul style="list-style-type: none"> <li>▪ Adverse Event Reporting and Analysis—CFSAN #7</li> </ul>	57
	CVM <ul style="list-style-type: none"> <li>▪ Safety Evaluation of New Animal Antimicrobials and Antimicrobial Resistance—CVM #4</li> <li>▪ Ensuring the Safety and Effectiveness of Marketed Animal Drugs, Special Dietary Feeds, and other Veterinary Medical Products—CVM #8</li> </ul>	69

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #2—Marketed Product Adverse Event Surveillance and Efficacy/Safety Assessment</b>		
	NCTR <ul style="list-style-type: none"> <li>▪ Scientific Computing: Informatics Support for Modern Panomics and Toxicology—NCTR #5</li> </ul>	80
a. Surveillance and characterization of antimicrobial susceptibility patterns of food-borne bacteria from retail meats	NCTR <ul style="list-style-type: none"> <li>▪ Rapid Detection of Food-Borne Pathogens—NCTR #4</li> </ul>	80
b. Product studies: Post-marketing study design and data review (e.g., studies required as a condition of product approval, other phase 4 studies, industry device studies required by CDRH under section 522)	CDER <ul style="list-style-type: none"> <li>▪ Active Safety Surveillance—CDER #7</li> </ul>	41
c. Population-based studies: Design/undertake population and meta-data studies (e.g., epidemiologic, sample surveys, lit searches, including use of data in marketing applications), studies on automated data bases of claims or electronic medical records for epidemiologic assessment of safety concerns.	CDER <ul style="list-style-type: none"> <li>▪ Active Safety Surveillance—CDER #7</li> </ul>	41
	CFSAN <ul style="list-style-type: none"> <li>▪ Regulatory Programs to Implement the Food Allergen Labeling and Consumer Protection Act (FALCPA) and Advancing Effective Interventions—CFSAN #3</li> <li>▪ Detection of Food-Borne Viruses—CFSAN #4</li> <li>▪ Prevention of Food-Borne Viral Diseases—CFSAN #5</li> </ul>	57
	CVM <ul style="list-style-type: none"> <li>▪ Review of Human Food Safety Issues in New Animal Drug Applications—CVM #2</li> </ul>	69
d. Monitoring for illegal sale of FDA-regulated products	CDER <ul style="list-style-type: none"> <li>▪ Risk-Based Inspectional Models—CDER #9</li> </ul>	41
e. Oversight of changes made to marketed devices		

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #2—Marketed Product Adverse Event Surveillance and Efficacy/Safety Assessment</b>		
2.3 Methods Development	CBER <ul style="list-style-type: none"> <li>▪ Predictive Biomarkers for Biologics Medical Products—CBER #1</li> <li>▪ New Approaches to Pre-Market Review of Gene Therapy Products—CBER #2</li> <li>▪ Pre-Market Review of Vaccine Therapies—CBER #4</li> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products—CBER #6</li> <li>▪ Post-Market Surveillance of Blood Products—CBER #14</li> <li>▪ Post-Market Surveillance and Quality Assurance of Biologic Medical Products—CBER #15</li> </ul>	3
	CDRH <ul style="list-style-type: none"> <li>▪ Adverse Event Detection, Data, and Analysis—CDRH #8</li> </ul>	25
	CDER <ul style="list-style-type: none"> <li>▪ Active Safety Surveillance—CDER #7</li> </ul>	41
	CFSAN <ul style="list-style-type: none"> <li>▪ Regulatory Programs to Implement the Food Allergen Labeling and Consumer Protection Act (FALCPA) and Advancing Effective Interventions—CFSAN #3</li> <li>▪ Adverse Event Reporting and Analysis—CFSAN #7</li> </ul>	57
	CVM <ul style="list-style-type: none"> <li>▪ Safety Evaluation of New Animal Antimicrobials and Antimicrobial Resistance—CVM #4</li> <li>▪ Ensuring the Safety and Effectiveness of Marketed Animal Drugs, Special Dietary Feeds, and other Veterinary Medical Products—CVM #8</li> <li>▪ Post-Marketing Surveillance and Data Analysis—CVM #10</li> </ul>	69
	NCTR <ul style="list-style-type: none"> <li>▪ Implementing Panomics in Regulatory Review—NCTR #2</li> <li>▪ Scientific Computing: Informatics Support for Modern Panomics and Toxicology—NCTR #5</li> </ul>	80

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #2—Marketed Product Adverse Event Surveillance and Efficacy/Safety Assessment</b>		
a. Develop analytical methods for signal detection and evaluation, design and undertake studies to evaluate signals	CDER <ul style="list-style-type: none"> <li>▪ Integrating Genomics Into Regulatory Activities—CDER #2</li> <li>▪ Understanding the Genetic Basis of Serious Adverse Events—CDER #3</li> <li>▪ Identification and Qualification of Biomarkers for Safety and Efficacy—CDER #6</li> </ul>	41
	CFSAN <ul style="list-style-type: none"> <li>▪ Detection of Food-Borne Viruses—CFSAN #4</li> <li>▪ Prevention of Food-Borne Viral Diseases—CFSAN #5</li> </ul>	57
	NCTR <ul style="list-style-type: none"> <li>▪ Rapid Detection of Food-Borne Pathogens—NCTR #4</li> </ul>	80
b. Research and analysis to develop and qualify new safety biomarkers based on surveillance information	CBER <ul style="list-style-type: none"> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products—CBER #6</li> </ul>	3
	CDER <ul style="list-style-type: none"> <li>▪ Integrating Genomics Into Regulatory Activities—CDER #2</li> <li>▪ Understanding the Genetic Basis of Serious Adverse Events—CDER #3</li> <li>▪ Identification and Qualification of Biomarkers for Safety and Efficacy—CDER #6</li> </ul>	41
	CFSAN <ul style="list-style-type: none"> <li>▪ Detection of Food-Borne Viruses—CFSAN #4</li> <li>▪ Prevention of Food-Borne Viral Diseases—CFSAN #5</li> </ul>	57
	CVM <ul style="list-style-type: none"> <li>▪ Review of Human Food Safety Issues in New Animal Drug Applications—CVM #2</li> </ul>	69
	NCTR <ul style="list-style-type: none"> <li>▪ Rapid Detection of Food-Borne Pathogens—NCTR #4</li> </ul>	80

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #2—Marketed Product Adverse Event Surveillance and Efficacy/Safety Assessment</b>		
c. Develop sampling and detection methods for surveillance for priority chemical, microbiological, and radiological agents in vulnerable foods	CBER <ul style="list-style-type: none"> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products—CBER #6</li> </ul>	3
	CFSAN <ul style="list-style-type: none"> <li>▪ Detection of Food-Borne Viruses—CFSAN #4</li> <li>▪ Prevention of Food-Borne Viral Diseases—CFSAN #5</li> </ul>	57
	CVM <ul style="list-style-type: none"> <li>▪ Review of Human Food Safety Issues in New Animal Drug Applications—CVM #2</li> </ul>	69
	NCTR <ul style="list-style-type: none"> <li>▪ Rapid Detection of Food-Borne Pathogens—NCTR #4</li> </ul>	80
2.4 Take Action on Safety/Efficacy Problems	CBER <ul style="list-style-type: none"> <li>▪ Post-Market Surveillance of Blood Products—CBER #14</li> <li>▪ Post-Market Surveillance and Quality Assurance of Biologic Medical Products—CBER #15</li> </ul>	3
	CDER <ul style="list-style-type: none"> <li>▪ Risk-Based Inspectional Models—CDER #9</li> </ul>	41
	CFSAN <ul style="list-style-type: none"> <li>▪ Regulatory Programs to Implement the Food Allergen Labeling and Consumer Protection Act (FALCPA) and Advancing Effective Interventions—CFSAN #3</li> </ul>	57
a. Investigations, follow up with sponsors		
b. Review manufacturer corrective action plans, design and evaluate risk management programs	CDRH <ul style="list-style-type: none"> <li>▪ Reuse of Single Use Devices (SUDs)—CDRH #2</li> </ul>	25

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #2—Marketed Product Adverse Event Surveillance and Efficacy/Safety Assessment</b>		
2.5 Implement and Evaluate Risk Communications (public announcements, safety alerts, label changes), develop risk communication materials appropriate to specific audiences, dissemination, implement actions such as label changes)	CBER <ul style="list-style-type: none"> <li>▪ Post-Market Surveillance of Blood Products—CBER #14</li> <li>▪ Post-Market Surveillance and Quality Assurance of Biologic Medical Products—CBER #15</li> </ul>	3
	CDRH <ul style="list-style-type: none"> <li>▪ Risk Communication—CDRH #6</li> </ul>	25
	CDER <ul style="list-style-type: none"> <li>▪ Risk Communications—CDER #14</li> </ul>	41
	CFSAN <ul style="list-style-type: none"> <li>▪ Regulatory Programs to Implement the Food Allergen Labeling and Consumer Protection Act (FALCPA) and Advancing Effective Interventions—CFSAN #3</li> <li>▪ Detection of Food-Borne Viruses—CFSAN #4</li> <li>▪ Prevention of Food-Borne Viral Diseases—CFSAN #5</li> </ul>	57
	CVM <ul style="list-style-type: none"> <li>▪ Emerging Technologies in the Review of New Animal Drug Applications—CVM #1</li> <li>▪ Review of Human Food Safety Issues in New Animal Drug Applications—CVM #2</li> <li>▪ Ensuring the Safety and Effectiveness of Marketed Animal Drugs, Special Dietary Feeds, and other Veterinary Medical Products—CVM #8</li> </ul>	69
2.6 Emergency Response Preparation and Crisis Management	CBER <ul style="list-style-type: none"> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products—CBER #6</li> <li>▪ Diagnostic Testing of Biologics Medical Products—CBER #12</li> <li>▪ Post-Market Surveillance of Blood Products—CBER #14</li> <li>▪ Post-Market Surveillance and Quality Assurance of Biologic Medical Products—CBER #15</li> </ul>	3

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #2—Marketed Product Adverse Event Surveillance and Efficacy/Safety Assessment</b>		
a. Work with domestic and international partners to prepare for and respond to public health threats and crises (e.g., pandemic, counterterrorism)	CFSAN <ul style="list-style-type: none"> <li>▪ Detection of Food-Borne Viruses—CFSAN #4</li> <li>▪ Prevention of Food-Borne Viral Diseases—CFSAN #5</li> </ul>	57
	CVM <ul style="list-style-type: none"> <li>▪ Review of Human Food Safety Issues in New Animal Drug Applications—CVM #2</li> </ul>	69
	NCTR <ul style="list-style-type: none"> <li>▪ Rapid Detection of Food-Borne Pathogens—NCTR #4</li> </ul>	80
b. Work with the industry on procedures to address terrorism and compliance with any relevant regulations	CFSAN <ul style="list-style-type: none"> <li>▪ Detection of Food-Borne Viruses—CFSAN #4</li> <li>▪ Prevention of Food-Borne Viral Diseases—CFSAN #5</li> </ul>	57
2.7 Standards/Guidance Development	CBER <ul style="list-style-type: none"> <li>▪ Predictive Biomarkers for Biologics Medical Products—CBER #1</li> <li>▪ Pre-Market Review of Vaccine Therapies—CBER #4</li> <li>▪ Post-Market Surveillance of Blood Products—CBER #14</li> <li>▪ Post-Market Surveillance and Quality Assurance of Biologic Medical Products—CBER #15</li> </ul>	3
	CDRH <ul style="list-style-type: none"> <li>▪ Reuse of Single Use Devices (SUDs)—CDRH #2</li> <li>▪ Adverse Event Detection, Data, and Analysis—CDRH #8</li> <li>▪ Human Factors—CDRH #10</li> <li>▪ Combination Products—CDRH #12</li> <li>▪ Medical Imaging and Computer-aided Diagnosis—CDRH #13</li> </ul>	25
	CDER <ul style="list-style-type: none"> <li>▪ Active Safety Surveillance—CDER #7</li> <li>▪ Risk-Based Inspectional Models—CDER #9</li> <li>▪ Better Tools for Pediatric Drug Development—CDER #10</li> </ul>	41

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #2—Marketed Product Adverse Event Surveillance and Efficacy/Safety Assessment</b>		
	CFSAN <ul style="list-style-type: none"> <li>▪ Regulatory Programs to Implement the Food Allergen Labeling and Consumer Protection Act (FALCPA) and Advancing Effective Interventions—CFSAN #3</li> </ul>	57
	CVM <ul style="list-style-type: none"> <li>▪ Ensuring the Safety and Effectiveness of Marketed Animal Drugs, Special Dietary Feeds, and other Veterinary Medical Products—CVM #8</li> <li>▪ Post-Marketing Surveillance and Data Analysis—CVM #10</li> </ul>	69
	NCTR <ul style="list-style-type: none"> <li>▪ Implementing Panomics in Regulatory Review—NCTR #2</li> <li>▪ Scientific Computing: Informatics Support for Modern Panomics and Toxicology—NCTR #5</li> </ul>	80
a. Scientific Standards—development of technical and scientific standards, domestic and international harmonization of such standards	CBER <ul style="list-style-type: none"> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products—CBER #6</li> </ul>	3
	CDER <ul style="list-style-type: none"> <li>▪ Integrating Genomics Into Regulatory Activities—CDER #2</li> <li>▪ Understanding the Genetic Basis of Serious Adverse Events—CDER #3</li> <li>▪ Identification and Qualification of Biomarkers for Safety and Efficacy—CDER #6</li> </ul>	41
	CFSAN <ul style="list-style-type: none"> <li>▪ Detection of Food-Borne Viruses—CFSAN #4</li> <li>▪ Prevention of Food-Borne Viral Diseases—CFSAN #5</li> </ul>	57
	CVM <ul style="list-style-type: none"> <li>▪ Review of Human Food Safety Issues in New Animal Drug Applications—CVM #2</li> <li>▪ Safety Evaluation of New Animal Antimicrobials and Antimicrobial Resistance—CVM #4</li> </ul>	69

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #2—Marketed Product Adverse Event Surveillance and Efficacy/Safety Assessment</b>		
b. Data Standards—development of data standards (e.g., electronic standards for submission of adverse event information), domestic and international development and harmonization of such standards	CDER <ul style="list-style-type: none"> <li>▪ Integrating Genomics Into Regulatory Activities—CDER #2</li> <li>▪ Understanding the Genetic Basis of Serious Adverse Events—CDER #3</li> <li>▪ Identification and Qualification of Biomarkers for Safety and Efficacy—CDER #6</li> </ul>	41
	CVM <ul style="list-style-type: none"> <li>▪ Safety Evaluation of New Animal Antimicrobials and Antimicrobial Resistance –CVM #4</li> </ul>	69



Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #3—Ensuring Marketed Product Quality and Safety</b>		
c. Implement/Oversee Quality Management Programs (cGMPs, HAACP, QSR), encourage adoption of robust quality systems (to detect, correct, and prevent product defects)	CDER <ul style="list-style-type: none"> <li>▪ Bioequivalence Science—CDER #12</li> <li>▪ Manufacturing Science—CDER #13</li> </ul>	41
	CFSAN <ul style="list-style-type: none"> <li>▪ Detection of Food-Borne Viruses—CFSAN #4</li> <li>▪ Prevention of Food-Borne Viral Diseases—CFSAN #5</li> </ul>	57
	CVM <ul style="list-style-type: none"> <li>▪ Manufacturing and Chemistry Review of New Animal Drug Applications—CVM #3</li> </ul>	69
d. Approval and oversight of accreditation bodies and inspectors for products/manufacturing facilities		
e. Oversight of marketed products (e.g., design and evaluate risk management programs, receive and assess product deviation reports, annual reports, published literature, safety analysis of cosmetic ingredients), investigate complaints	CDER <ul style="list-style-type: none"> <li>▪ Risk Communication—CDRH #6</li> </ul>	41
	CFSAN <ul style="list-style-type: none"> <li>▪ Safety of Cosmetics—CFSAN #6</li> </ul>	57

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #3—Ensuring Marketed Product Quality and Safety</b>		
3.2 Methods Development (develop test methods, forensic and other, e.g., develop/validate methods for bacterial antimicrobial susceptibility, drug residues and prohibited animal proteins in animal-derived foods and animal feeds)	CBER <ul style="list-style-type: none"> <li>▪ Predictive Biomarkers for Biologics Medical Products—CBER #1</li> <li>▪ New Approaches to Pre-Market Review of Gene Therapy Products—CBER #2</li> <li>▪ Evaluation Methods for Tissue Product Quality and Safety—CBER #3</li> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products—CBER #6</li> <li>▪ Safety Approaches and Surveillance Methods for Blood Products—CBER #8</li> <li>▪ Pre-Market Review and Product Quality Testing of Vaccine Therapies—CBER #9</li> <li>▪ Product Quality &amp; Safety Standards for Biologics Medical Products—CBER #13</li> <li>▪ Statistical Approaches to Biologic Product Quality and Safety—CBER #16</li> </ul>	3
	CDER <ul style="list-style-type: none"> <li>▪ Safety, Efficacy and Characterization of Complex Biologic Products—CDER #11</li> <li>▪ Manufacturing Science—CDER #13</li> </ul>	41
	CFSAN <ul style="list-style-type: none"> <li>▪ Regulatory Programs to Implement the Food Allergen Labeling and Consumer Protection Act (FALCPA) and Advancing Effective Interventions—CFSAN #3</li> <li>▪ Detection of Food-Borne Viruses—CFSAN #4</li> <li>▪ Prevention of Food-Borne Viral Diseases—CFSAN #5</li> <li>▪ Safety of Cosmetics—CFSAN #6</li> </ul>	57

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #3—Ensuring Marketed Product Quality and Safety</b>		
	<p>CVM</p> <ul style="list-style-type: none"> <li>▪ Review of Human Food Safety Issues in New Animal Drug Applications—CVM #2</li> <li>▪ Safety Evaluation of New Animal Antimicrobials and Antimicrobial Resistance—CVM #4</li> <li>▪ Post-Market Surveillance to Ensure that Animal Feed Products Derived from Waste/Co-products from Agricultural/Industrial Processes is Safe for Use in Animal Feed—CVM #6</li> <li>▪ Evaluation and Prevention of Contamination of Animal Feed with Hazardous Materials from Rendering Facilities—CVM #9</li> </ul>	69
	<p>NCTR</p> <ul style="list-style-type: none"> <li>▪ Implementing Panomics in Regulatory Review—NCTR #2</li> <li>▪ Rapid Detection of Food-Borne Pathogens—NCTR #4</li> <li>▪ Scientific Computing: Informatics Support for Modern Panomics and Toxicology—NCTR #5</li> </ul>	80
3.3 Industry Outreach and Education	<p>CDRH</p> <ul style="list-style-type: none"> <li>▪ Modeling Biological Processes—CDRH #5</li> </ul>	25
	<p>CDER</p> <ul style="list-style-type: none"> <li>▪ Risk-Based Inspectional Models—CDER #9</li> <li>▪ Safety, Efficacy and Characterization of Complex Biologic Products—CDER #11</li> <li>▪ Bioequivalence Science—CDER #12</li> <li>▪ Manufacturing Science—CDER #13</li> </ul>	41
	<p>CFSAN</p> <ul style="list-style-type: none"> <li>▪ Regulatory Programs to Implement the Food Allergen Labeling and Consumer Protection Act (FALCPA) and Advancing Effective Interventions—CFSAN #3</li> <li>▪ Detection of Food-Borne Viruses—CFSAN #4</li> <li>▪ Prevention of Food-Borne Viral Diseases—CFSAN #5</li> <li>▪ Safety of Cosmetics—CFSAN #6</li> </ul>	57

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #3—Ensuring Marketed Product Quality and Safety</b>		
	CVM <ul style="list-style-type: none"> <li>▪ Manufacturing and Chemistry Review of New Animal Drug Applications—CVM #3</li> <li>▪ Evaluation and Prevention of Contamination of Animal Feed with Hazardous Materials from Rendering Facilities—CVM #9</li> </ul>	69
3.4 Implement and Evaluate Risk Communications	CDRH <ul style="list-style-type: none"> <li>▪ Risk Communication—CDRH #6</li> <li>▪ Human Factors—CDRH #10</li> </ul>	25
	CFSAN <ul style="list-style-type: none"> <li>▪ Consumer Understanding of Nutrition and Food Safety Information—CFSAN #2</li> <li>▪ Regulatory Programs to Implement the Food Allergen Labeling and Consumer Protection Act (FALCPA) and Advancing Effective Interventions—CFSAN #3</li> <li>▪ Detection of Food-Borne Viruses—CFSAN #4</li> <li>▪ Prevention of Food-Borne Viral Diseases—CFSAN #5</li> <li>▪ Safety of Cosmetics—CFSAN #6</li> </ul>	57
	CVM <ul style="list-style-type: none"> <li>▪ Manufacturing and Chemistry Review of New Animal Drug Applications—CVM #3</li> <li>▪ Safety Evaluation of New Animal Antimicrobials and Antimicrobial Resistance—CVM #4</li> <li>▪ Evaluation and Prevention of Contamination of Animal Feed with Hazardous Materials from Rendering Facilities—CVM #9</li> </ul>	69
3.5 Product Shortage Activities (receive reports, investigate, medical necessity determination, potential action, consultation)		

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #3—Ensuring Marketed Product Quality and Safety</b>		
3.6 Review Electronic Product Radiation Safety Reports		
a. review product conformance to applicable radiation safety performance standards		
b. review manufacturer quality control testing program for ability to ensure product conformance and safety	CFSAN <ul style="list-style-type: none"> <li>▪ Detection of Food-Borne Viruses—CFSAN #4</li> <li>▪ Prevention of Food-Borne Viral Diseases—CFSAN #5</li> </ul>	57
	CVM <ul style="list-style-type: none"> <li>▪ Manufacturing and Chemistry Review of New Animal Drug Applications—CVM #3</li> </ul>	69
3.7 Advertising Review and Monitoring	CDER <ul style="list-style-type: none"> <li>▪ Risk Communication—CDRH #6</li> <li>▪ Risk Communications—CDER #14</li> </ul>	41
	CFSAN <ul style="list-style-type: none"> <li>▪ Safety of Cosmetics—CFSAN #6</li> <li>▪ Regulatory Programs to Implement the Food Allergen Labeling and Consumer Protection Act (FALCPA) and Advancing Effective Interventions—CFSAN #3</li> </ul>	57
3.8 Facility and Product Registration/Listing Activities	CVM <ul style="list-style-type: none"> <li>▪ Maintain a Publicly Available Inventory of All Marketed Animal Drugs to Ensure Adequate Information is Available for Regulatory Activity and Customer Support—CVM #7</li> <li>▪ Ensuring the Safety and Effectiveness of Marketed Animal Drugs, Special Dietary Feeds, and other Veterinary Medical Products—CVM #8</li> </ul>	69
a. Review facility registrations, ensure completeness, assign unique registration number		
b. Review product listings, review the product listing for completeness, assign the owner/operator a unique listing number	CFSAN <ul style="list-style-type: none"> <li>▪ Safety of Cosmetics—CFSAN #6</li> </ul>	57

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #3—Ensuring Marketed Product Quality and Safety</b>		
c. Review export certification requests: confirm products being exported: are freely marketed in the US; are in compliance with US and importing country's requirements; meet certain national or international standards, such as quality standards; do not contain specific contaminants		
3.9 Standards/Guidance Development	CBER <ul style="list-style-type: none"> <li>▪ Predictive Biomarkers for Biologics Medical Products—CBER #1</li> <li>▪ New Approaches to Pre-Market Review of Gene Therapy Products—CBER #2</li> <li>▪ Evaluation Methods for Tissue Product Quality and Safety—CBER #3</li> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products—CBER #6</li> <li>▪ Safety Approaches and Surveillance Methods for Blood Products—CBER #8</li> <li>▪ Pre-Market Review and Product Quality Testing of Vaccine Therapies—CBER #9</li> <li>▪ Product Quality &amp; Safety Standards for Biologics Medical Products—CBER #13</li> </ul>	3
	CDRH <ul style="list-style-type: none"> <li>▪ Safety of Medical Products Containing Software—CDRH #1</li> <li>▪ Reuse of Single Use Devices (SUDs)—CDRH #2</li> <li>▪ Modeling Biological Processes—CDRH #5</li> <li>▪ Device Applications of Genomics—CDRH #7</li> <li>▪ Nanotechnology—CDRH #9</li> <li>▪ Closed Loop Systems—CDRH #11</li> <li>▪ Combination Products—CDRH #12</li> </ul>	25

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #3—Ensuring Marketed Product Quality and Safety</b>		
	CDER <ul style="list-style-type: none"> <li>▪ Risk Communication—CDRH #6</li> <li>▪ Risk-Based Inspectional Models—CDER #9</li> <li>▪ Safety, Efficacy and Characterization of Complex Biologic Products—CDER #11</li> <li>▪ Bioequivalence Science—CDER #12</li> <li>▪ Manufacturing Science—CDER #13</li> <li>▪ Risk Communications—CDER #14</li> </ul>	41
	CFSAN <ul style="list-style-type: none"> <li>▪ Regulatory Programs to Implement the Food Allergen Labeling and Consumer Protection Act (FALCPA) and Advancing Effective Interventions—CFSAN #3</li> <li>▪ Consumer Understanding of Nutrition and Food Safety Information—CFSAN #2</li> <li>▪ Food Production Sciences: Risk Mitigation at the Source—CFSAN #1</li> </ul>	57
	CVM <ul style="list-style-type: none"> <li>▪ Post market Surveillance to Ensure that Animal Feed Products Derived from Waste/Co-products from Agricultural/Industrial Processes is Safe for Use in Animal Feed—CVM #6</li> <li>▪ Evaluation and Prevention of Contamination of Animal Feed with Hazardous Materials from Rendering Facilities—CVM #9</li> </ul>	69
	NCTR <ul style="list-style-type: none"> <li>▪ Scientific Computing: Informatics Support for Modern Panomics and Toxicology—NCTR #5</li> </ul>	80

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Core Activity #3—Ensuring Marketed Product Quality and Safety</b>		
a. Scientific Standards—development of technical and scientific standards, domestic and international harmonization of such standards (e.g., packaging standards, food safety standards, food processing technologies, time/temperature for pasteurization, guidelines under heightened threat alerts, hospital transfusion services)	CBER <ul style="list-style-type: none"> <li>▪ Pre-Market Guidance and Reference Standards for Blood Products—CBER #6</li> <li>▪ Safety Approaches and Surveillance Methods for Blood Products—CBER #8</li> <li>▪ Pre-Market Review and Product Quality Testing of Vaccine Therapies—CBER #9</li> </ul>	3
	CFSAN <ul style="list-style-type: none"> <li>▪ Safety of Cosmetics—CFSAN #6</li> <li>▪ Detection of Food-Borne Viruses—CFSAN #4</li> <li>▪ Prevention of Food-Borne Viral Diseases—CFSAN #5</li> </ul>	57
	NCTR <ul style="list-style-type: none"> <li>▪ Rapid Detection of Food-Borne Pathogens—NCTR #4</li> </ul>	80
b. Data Standards—development of data standards (e.g., electronic standards for listing information), domestic and international development and harmonization of such standards	CDRH <ul style="list-style-type: none"> <li>▪ Adverse Event Detection, Data, and Analysis—CDRH #8</li> </ul>	25
	CFSAN <ul style="list-style-type: none"> <li>▪ Safety of Cosmetics—CFSAN #6</li> </ul>	57
	CVM <ul style="list-style-type: none"> <li>▪ Maintain a Publicly Available Inventory of All Marketed Animal Drugs to Ensure Adequate Information is Available for Regulatory Activity and Customer Support—CVM #7</li> <li>▪ Ensuring the Safety and Effectiveness of Marketed Animal Drugs, Special Dietary Feeds, and other Veterinary Medical Products—CVM #8</li> </ul>	69

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Supporting Activities</b>		
S.1 Bioinformatics Activities	CDRH <ul style="list-style-type: none"> <li>▪ Adverse Event Detection, Data, and Analysis—CDRH #8</li> </ul>	25
	CFSAN <ul style="list-style-type: none"> <li>▪ Regulatory Programs to Implement the Food Allergen Labeling and Consumer Protection Act (FALCPA) and Advancing Effective Interventions—CFSAN #3</li> </ul>	57
	CVM <ul style="list-style-type: none"> <li>▪ Evaluation of Novel Animal Feed Substances for Safety and Utility—CVM #5</li> <li>▪ Post market Surveillance to Ensure that Animal Feed Products Derived from Waste/Co-products from Agricultural/Industrial Processes is Safe for Use in Animal Feed—CVM #6</li> <li>▪ Maintain a Publicly Available Inventory of All Marketed Animal Drugs to Ensure Adequate Information is Available for Regulatory Activity and Customer Support—CVM #7</li> <li>▪ Ensuring the Safety and Effectiveness of Marketed Animal Drugs, Special Dietary Feeds, and other Veterinary Medical Products—CVM #8</li> <li>▪ Post-Marketing Surveillance and Data Analysis—CVM #10</li> </ul>	69
	NCTR <ul style="list-style-type: none"> <li>▪ Scientific Computing: Informatics Support for Modern Panomics and Toxicology—NCTR #5</li> </ul>	80
a. Develop and maintain IT systems to allow sponsors to submit marketing applications to FDA electronically (including capacity to capture data from pre-market submissions and reviews and provide searchability for future reviews and guidance development)	CVM <ul style="list-style-type: none"> <li>▪ Emerging Technologies in the Review of New Animal Drug Applications—CVM #1</li> </ul>	69
	NCTR <ul style="list-style-type: none"> <li>▪ Analytic Tools and Expertise for Regulatory Support Due to Pace of Change in Disease Patterns and Technology Use—NCTR #1</li> </ul>	80

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Supporting Activities</b>		
b. Develop and maintain IT systems to receive and process adverse event reports, product deviation/failure reports, and other safety-related report electronically from sponsors, consumers, and others.	CVM <ul style="list-style-type: none"> <li>▪ Emerging Technologies in the Review of New Animal Drug Applications—CVM #1</li> </ul>	69
c. Develop and maintain IT systems that link to external systems that monitor or evaluate adverse events, or to support other data exchanges (e.g., link to CDC systems for information on food contamination outbreaks, infectious disease outbreaks, weekly transfer of certified mammography facility data to CMS, CFSAN data exchanges with USDA, data from CDC on vaccines, tissues)		
d. Develop and maintain electronic dictionaries: product names and classes; adverse event classification; product types.		
e. Develop and maintain IT systems that support product and facility listing/registration activities		
f. Develop and maintain IT systems that allow access to and processing of information from large adverse event/medical databases		
g. Develop and maintain IT systems to support risk communications to stakeholders (e.g., robust list-serves)		
h. Develop and maintain IT systems that support internal information dissemination (about FDA policies and updates, scientific issues, public health matters)		
i. Develop and maintain IT systems to manage regulatory development (tracking, capture of public comment)		
j. Develop and maintain an IT system to supports		

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Supporting Activities</b>		
specialized scientific tools for regulatory review and research		
S.2 Enforcement	CDRH <ul style="list-style-type: none"> <li>▪ Adverse Event Detection, Data, and Analysis—CDRH #8</li> </ul>	25
	CFSAN <ul style="list-style-type: none"> <li>▪ Regulatory Programs to Implement the Food Allergen Labeling and Consumer Protection Act (FALCPA) and Advancing Effective Interventions—CFSAN #3</li> </ul>	57
a. Legal actions	CFSAN <ul style="list-style-type: none"> <li>▪ Detection of Food-Borne Viruses—CFSAN #4</li> <li>▪ Prevention of Food-Borne Viral Diseases—CFSAN #5</li> </ul>	57
b. Investigations	CFSAN <ul style="list-style-type: none"> <li>▪ Detection of Food-Borne Viruses—CFSAN #4</li> <li>▪ Prevention of Food-Borne Viral Diseases—CFSAN #5</li> </ul>	57
c. Recalls	CFSAN <ul style="list-style-type: none"> <li>▪ Detection of Food-Borne Viruses—CFSAN #4</li> <li>▪ Prevention of Food-Borne Viral Diseases—CFSAN #5</li> </ul>	57
<b>S.3 Education</b> (of manufacturers, sponsors, clinical investigators, IRBs, medical community, consumers, etc.)	CDRH <ul style="list-style-type: none"> <li>▪ Reuse of Single Use Devices (SUDs)—CDRH #2</li> <li>▪ Failure Analysis (Device Materials)—CDRH #3</li> <li>▪ Modeling Biological Processes—CDRH #5</li> <li>▪ Risk Communication—CDRH #6</li> <li>▪ Device Applications of Genomics—CDRH #7</li> <li>▪ Adverse Event Detection, Data, and Analysis—CDRH #8</li> <li>▪ Nanotechnology—CDRH #9</li> <li>▪ Closed Loop Systems—CDRH #11</li> <li>▪ Combination Products—CDRH #12</li> <li>▪ Medical Imaging and Computer-aided Diagnosis—CDRH #13</li> </ul>	25
	CFSAN	57

Regulatory Activity	Cross-Reference to Centers' Priority Scientific Limitations	Page #
<b>Supporting Activities</b>		
	<ul style="list-style-type: none"> <li>▪ Consumer Understanding of Nutrition and Food Safety Information—CFSAN #2</li> <li>▪ Regulatory Programs to Implement the Food Allergen Labeling and Consumer Protection Act (FALCPA) and Advancing Effective Interventions—CFSAN #3</li> <li>▪ Detection of Food-Borne Viruses—CFSAN #4</li> <li>▪ Prevention of Food-Borne Viral Diseases—CFSAN #5</li> </ul>	
<b>S.4 Training FDA Personnel</b> (e.g., ongoing training in new science)	CDRH <ul style="list-style-type: none"> <li>▪ Safety of Medical Products Containing Software—CDRH #1</li> <li>▪ Failure Analysis (Device Materials)—CDRH #3</li> <li>▪ Risk Communication—CDRH #6</li> <li>▪ Adverse Event Detection, Data, and Analysis—CDRH #8</li> </ul>	25
	CFSAN <ul style="list-style-type: none"> <li>▪ Regulatory Programs to Implement the Food Allergen Labeling and Consumer Protection Act (FALCPA) and Advancing Effective Interventions—CFSAN #3</li> <li>▪ Detection of Food-Borne Viruses—CFSAN #4</li> <li>▪ Prevention of Food-Borne Viral Diseases—CFSAN #5</li> </ul>	57
S.5 ORA Field Resources	CDRH <ul style="list-style-type: none"> <li>▪ Adverse Event Detection, Data, and Analysis—CDRH #8</li> </ul>	25
	CFSAN <ul style="list-style-type: none"> <li>▪ Regulatory Programs to Implement the Food Allergen Labeling and Consumer Protection Act (FALCPA) and Advancing Effective Interventions—CFSAN #3</li> <li>▪ Detection of Food-Borne Viruses—CFSAN #4</li> <li>▪ Prevention of Food-Borne Viral Diseases—CFSAN #5</li> </ul>	57