NCTR
Strategic Plan
2009 - 2013

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Vision

NCTR is an internationally recognized FDA research center that provides innovative and vital scientific technology, training, and technical expertise to improve public health. NCTR—in partnership with researchers from government, academia, and industry—develops, refines, and applies current and emerging technologies to improve safety evaluations of FDA-regulated products. NCTR fosters national and international collaborations to improve and protect public health and enhance the quality of life for the American people.

Mission

NCTR conducts peer-reviewed scientific research in support of the FDA mission and provides expert technical advice and training that enables FDA to make sound science-based regulatory decisions and improve the health of the American people. The research at NCTR supports FDA's goals: 1) to understand critical biological events in the expression of toxicity, 2) to develop and characterize methods, and incorporate new technologies to improve the assessment of human exposure, susceptibility, and risk, and 3) to increase the understanding of the interaction between genetics, metabolism, and nutrition.

NCTR is dedicated to supporting the FDA mission to protect and promote public health by:

- providing innovative and interdisciplinary research that promotes personal and public health .

- developing novel translational research approaches to provide FDA/DHHS with sound scientific infrastructure and multidisciplinary scientific expertise targeted towards addressing critical Agency, Department, and public-health needs such as personalized nutrition and medicine, bioimaging, systems biology, bioinformatics, nanotechnology, food protection technologies, and biomarker development

- engaging with scientists across FDA and other government agencies, industry, and academia in cooperative learning to strengthen the scientific foundations vital to developing sound regulatory policy and leveraging resources in order to promote the international standardization and global harmonization of regulatory science

- Participating in or leading national and international consortia for the development of harmonized standards for technologies and methods in risk assessment and for personal and public health

Strategic Goals

To accomplish its mission, NCTR has established five strategic goals:

Goal 1: **Advance scientific approaches and tools to promote personalized nutrition and medicine for the public**

Goal 2: **Develop science-based best-practice standards, guidance, and tools to incorporate toxicological advancements that improve the regulatory process**.

Goal 3: **Conduct research and develop strategic technologies to protect the food supply**

Goal 4: **Conduct bioinformatics research and development in support of FDA's regulatory mission**

Goal 5: **Strengthen and improve scientific and human capital management and expand training and outreach to retain and train scientific experts critical to address FDA's scientific needs**

Objectives and Strategies

Goal 1: Advance scientific approaches and tools to promote personalized nutrition and medicine for the public

In response to an identified need for personalized nutrition and medicine, FDA is committed to accelerating the development of safer and more effective 1) interventions for maintaining health that are based on the nutritional needs of an individual rather than "one-size-fits-all" recommendations for foods, and 2) individualized medical-product therapies. Recent advances in biotechnology have accelerated research on the development of molecular biomarkers for the diagnosis and treatment of disease. This research is a vital component of the FDA mission, especially in the area of incorporating pharmacogenomics and nutrigenomics into advancing personalized nutrition and medicine. Additionally, many interactions of foods, nutrients, and dietary supplements in individuals can now be characterized and this information can be used to address safety and health issues.

NCTR will conduct a broad range of research involving traditional approaches and novel systems-biology assessments for characterizing biomarkers for an individual's susceptibility to toxicants, disease risk, and health status. Such knowledge will aid the Agency in assessing the potential risk for optimizing personal and public health. NCTR will use new approaches including mathematical prediction and nutrigenomics to understand better how individual characteristics affect responses to foods, nutrients, dietary supplements and their interactions with toxicants and drugs.

Objectives and Supporting Strategies for Goal 1:

Objective 1.1 Improve the understanding of complex biological systems to guide the development and application of personalized nutrition and medicine

Strategies for Implementation

- Develop and evaluate omic approaches for identifying individuals of differing genetic and environmental susceptibility
- Design, adapt, and develop research tools (software) and databases for measuring nutrient intakes and physical activity
- Apply noninvasive or minimally-invasive imaging and omic technologies for defining normal and abnormal physiology, responses, and safety of toxicants, nutrients, dietary supplements, and other bioactive substances
- Develop approaches to assess genetic differences of individual and/or intergroup variability in relationship to metabolism, toxicity, efficacy, and/or susceptibility to adverse reactions to regulated products
- Obtain omic data from treated and untreated surrogate organisms and humans using an integrated systems-biology approach with *in silico*, *in vitro*, and *in vivo* models
- Design, develop, and conduct studies to understand more fully organ-specific (e.g., liver, kidney, cardiovascular, nervous system) health outcomes

Objective 1.2 Develop biomarkers and biometrical methods to aid in the effective characterization of consumer risks and benefits

Strategies for Implementation

- Develop, evaluate, and apply methods to measure and assess risk associated with regulated products for adverse outcomes such as cancer, developmental, reproductive, and neurological toxicity, and other chronic diseases
- Identify and validate genomic components and responses to diet and lifestyle involved in gender differences affecting drug, efficacy, and safety

Objective 1.3 Develop methods to monitor and predict interactions between human microbiota, antimicrobial agents, food additives, dietary supplements, and probiotics

Strategy for Implementation

- Evaluate the interaction of intestinal microbiota with drugs, dietary supplements, and probiotic compounds with a focus on differences among individuals
- Introduce concepts and technologies for assessing individual risk by using emerging knowledge and data from the human and animal genome and haplotype map projects
- Assess the impact of differing nutrient intakes on risk factors for toxicants and drugs using experimental paradigms that systemically alter diet and expression of genotype in model systems

Objective 1.4 Develop methods to analyze, understand, and contribute to the reduction of disparities among individuals of different ancestral populations

Strategies for Implementation

- Analyze candidate gene and/or genomic architecture contributing to differences in response to diet and drug treatments among individuals of diverse ethnic groups
- Enhance utilization of community-based participatory research to develop interventions to reduce disparities among subpopulations by optimizing nutrient intakes and treatment of disease by individualizing prevention and medical strategies.

Outcomes:

- Comprehensive toxicological evaluations of regulated *compounds*[*] (science important to the risk-assessment process) completed — FY 2009-2010
- International collaborations established for comparing biological responses of different genetic make-ups to foods, drugs, and lifestyle — FY 2009-2010
- Software and databases for nutrient assessments and physical activity measurements developed through intra- and interagency collaborations — FY 2009-2012

[*] *Compounds:* Aloe vera (oral), Aloe vera (topical), retinal palmitate, alpha & beta-hydroxy acids (topical), acrylamide and glycidamide (oral), ethinyl estradiol (oral), nonylphenol (oral), antiretroviral drugs (transplacental)

• Biometrical methods for class-prediction algorithms for biomarkers defining phenotypes including health and disease states developed for use in risk evaluation of new compounds	FY 2009-2012
• Changes in the species composition of the human microbiota caused by exposure to nutrients, dietary supplements, drugs, and food additives evaluated to identify individual biomarkers of toxicity	FY 2009-2013
• Determination made on whether microbial metabolism of dietary supplements, drugs, and food additives alters the safety and efficacy of the ingested products	FY 2009-2011
• Bacterial contaminants from dietary supplements, drugs, and food additives identified and characterized for use in risk evaluation	FY 2009-2011
• New genomic, proteomic, and metabolomic methods for assessing product safety for individuals developed	FY 2010
• Assessment of the potential for using the quantification of specific oncogene mutations to determine therapeutic strategy completed	FY2013
• Strategy developed to draft guidelines for assessing an individual's responses to food and food components based on nutrigenomic and epigenomic research	FY 2012

Measures of Success:

- A translational, community-based research strategy for implementing personalized healthcare
- Development of research software tool(s) and database(s) for nutrient intake (calories in) and for measuring a person's average physical activity (calories out) over a defined period of time
- National and international collaborations, coordination, and harmonization for improving studies in personalized nutrition and medicine to assess health and disease
- Train FDA reviewers on assessment of new biometric review tools
- Guidance document issued for assessing an individual's responses to foods and food components developed in conjunction with the Product Centers as requested by such regulatory groups
- Identification and characterization of bacterial contaminants from dietary supplements, drugs, and food additives
- Publications or manuscripts describing whether microbial metabolism of dietary supplements, drugs, and food additives alters the safety and efficacy of the ingested products
- Publications in peer-reviewed journals and presentations at conferences
- Published toxicological evaluations of compounds regulated by FDA

Goal 2: Develop science-based best-practice standards, guidance, and tools to incorporate toxicological advancements that improve the regulatory process

An important function of the FDA is to identify risks associated with the use of food, food additives, food and feed contaminants, and medical products and devices. One FDA goal is to improve the translation of preclinical data on drugs and devices to advance clinical care, and reduce the occurrence of adverse events. Another goal is to understand and reduce the risk associated with food contaminants and constituents. NCTR responds to the research needs of the FDA Product Centers by using toxicological methods to identify the hazards, inform the mode of action assessment, quantify the dose-response for adverse effects, and provide mechanistic or predictive biomarkers to understand human risk.

NCTR utilizes its state-of-the-art animal facilities to conduct established and guideline-compliant animal bioassays to quantify the dose-response of animals to a test material. The organ system responding to the toxicity of the test article (e.g. neurotoxicity, hepatotoxicity) and the endpoint of the toxicity (e.g. cancer, behavior abnormalities, and necrosis) may vary depending on the test article; however, expertise exists at NCTR to determine the mechanism of action of the test article, and understand the translation of these endpoints to humans. In collaboration with the National Toxicology Program (NTP), toxicological studies on many compounds of regulatory interest to FDA (e.g. acrylamide, pediatric anesthetics, bisphenol A) are being conducted at NCTR. Particularly important is the need to rapidly respond to emerging needs of the NTP and FDA Product Centers.

In addition to the established assays for quantifying the toxicity of a test article, NCTR is developing more modern methods and tools (e.g. *in vitro* assays, genomics, proteomics, metabolomics, and imaging) to support or replace the established bioassays. These new tools are being used to identify hazards, quantify the hazard dose-response, and determine predictive biomarkers associated with the products regulated by FDA. To effectively support the analysis of large datasets generated using new technologies such as pharmacogenomics, proteomics, and metabolomics, NCTR scientists develop and enhance scientific analytical software in collaboration with colleagues from government, academia, and industry to advance the incorporation of these data analyses into the regulatory process. For example, NCTR has led a large research consortium, i.e., MicroArray Quality Control (MAQC) that has developed standards and recommendations for conducting pharmacogenomic and pharmacogenetic studies, with emphasis on regulatory applications such as biomarkers and clinical diagnostics and prognostics. Software developed at NCTR for microarray studies has been implemented for use in electronic submission of pharmacogenomics data to FDA.

Several new areas of focus at NCTR involve:

1. Understanding the toxicity of nanoscale materials as a consequence of intended or unintended exposure, which led to the development of the NCTR/ORA

Nanotechnology Core Facility

2. Gaining awareness of the toxicity involved with co-exposure to FDA-regulated products and simulated sunlight, which led to the development of the NTP/NCTR Phototoxicology Center located at NCTR
3. The development of real-time and noninvasive data collection over the lifetime of an organism using bioimaging with methods such as Magnetic Resonance Imaging (MRI), Magnetic Resonance Spectroscopy (MRS), and Positron Emission Tomography (PET)

Noninvasive imaging is the ideal medium for biomarker development because the methods can be used similarly in humans as in animals, thus minimizing the assumptions in data interpretation and reducing uncertainty during product development or risk assessment. Imaging approaches for safety assessment studies have not been routinely used because of the lack of guidelines for application to traditional studies and the need for biomarker development/validation. NCTR, working collaboratively with the FDA Center for Devices and Radiological Health/Office of Science and Engineering Laboratories, will apply bioimaging approaches to explore imaging biomarkers and also assist in developing guidances for biomarker validation to enhance the use of this technology in the safety assessment of FDA-regulated products.

Objectives and Supporting Strategies for Goal 2:

Objective 2.1 Improve the understanding of how regulated products interact with the human organism

Strategies for implementation

- Develop, evaluate, and compare *in vivo* and *in vitro* toxicity testing systems and computer-assisted toxicology knowledge bases to provide quantitative data for safety assessments that are relevant to humans
- Develop and utilize minimally invasive methods to identify biomarkers in preclinical evaluations.
- Identify, translate, and validate biomarkers in nonclinical and clinical studies to improve the scientific basis of hazard-identification strategies and disease identification and progression to improve public health
- Apply imaging techniques to identify toxicity in exposed populations

Objective 2.2 Use statistical approaches and advanced computer technologies to predict adverse events from existing data and to predict the risk of exposure to biologically active products

Strategies for implementation

- Integrate bioinformatics software into the Agency review processes
- Manage and integrate data from the new technologies (e.g., *in silico* modeling, genomics, proteomics, nutritional and physical activity assessments, metabolomics, imaging) with traditional toxicological data
- Develop *in silico* approaches for predictive toxicology
- Develop a mathematical framework for integrating human uncertainty factors and characterizing model uncertainties for probabilistic risk assessment of

regulated products
- Develop/improve statistical methods for analyzing nonclinical toxicity data such as those associated with cancer, development/reproduction, photo activation, nutrition, genomic changes, organ-specific liabilities, and neurological function
- Actively participate in collaboration with national and international groups to develop standards and recommendations for the use of new technologies

Objective 2.3 Identify and quantify the toxicological risks associated with regulated products using current approaches or developing new and improved quantitative experimental approaches

Strategies for implementation

- Utilize existing methods to identify and quantify hazards of and dose-responses for products of interest to the FDA Product Centers
- Extend the knowledge and predictivity of toxicological assays by determining the mechanism of action and applying translational studies using pharmacogenomic, proteomic, metabolomic, and imaging approaches, etc.
- Develop a better understanding of interactions between the environment (physical, social, nutritional) and regulated products to improve risk assessment
- Study the potential hazardous effects of co-exposure to sunlight and FDA-regulated products, especially to the skin
- Develop relevant animal models, biomarkers, and molecular genetic and epigenetic methods that will contribute to more accurate risk evaluations for cancer in humans
- Develop approaches to apply dose-response mode-of-action analyses in quantitative cancer-risk assessment
- Develop expertise with nanotechnology and the appropriate infrastructure to better understand and regulate consumer products containing nanomaterials
- Develop and mine comprehensive databases of behavioral studies to predict effects of neuroactive compounds on clinically relevant aspects of brain function
- Develop, evaluate, and apply improved methods for preclinical safety evaluation of investigational new drugs, including novel stains for detecting tissue/cellular pathology
- Initiate the assessment of the utility of imaging technology for monitoring toxicities
- Develop a centralized in-house genetic monitoring unit to ensure the genetic integrity of NCTR's conventional and transgenic rodent breeding colonies through frequent, cost-effective genotyping

Outcomes:

- Collaborations (e.g. FDA Product Centers, government agencies and industry) and working groups (e.g. the Hepatotoxicity Working Group) fostered to advance clinical care and preclinical safety testing by translating data from nutrition, medicine, and toxicity testing for both nonclinical and clinical situations — FY 2009-2013
- MicroArray Quality Control (MAQC) III project initiated and completed, — FY 2009-2010

with the goal of evaluating new generation sequencing technologies

- Critical toxicology data gaps in FDA risk-assessment models (e.g. melamine, bisphenol A) addressed to support FDA risk-management decisions — FY 2009-2013
- Custom microarray method for analysis of mitochondrial damage applied to regulated products**.** — FY 2009-2013
- Metabolic fluxes analysis capabilities for mechanistic markers of a) adverse events during applications to regulated products and b) disease processes developed — FY 2009-2011
- NCTR/FDA Imaging Center housing construction completed with MRI and microPET equipment in place and expertise established — FY 2009-2010
- NCTR and Arkansas Regional Laboratory/ORA Nanotechnology Core Facility established; equipment purchased; and expertise for toxicology studies on nanoscale materials established — FY 2009-2010
- Systems-biology approaches developed to determine the environmental fate of FDA-regulated products and that may impact food or drug safety — FY 2009-2013
- New strategy developed for using *in vivo* mutation data and other biomarkers to inform the mode-of-action for cancer induction — FY 2009-2012
- New flow-cytometric method developed that detects chemically induced somatic cell mutation for safety assessment of regulated products — FY 2009-2010
- Assessment as to whether mutagenic carcinogens can have thresholds or nonlinear dose-response curves completed — FY 2012-2013
- Determination as to whether the standard genetic toxicology battery is appropriate for evaluating the safety of nanomaterials completed — FY 2009-2013

Measures of Success:

- Comprehensive peer review to validate the research and its Agency impact through Science Advisory Board (SAB) oversight
- Scientific teams established with representatives from FDA Product Centers, government agencies, and industry to advance clinical care and preclinical safety testing
- Publications in peer-reviewed journals and presentations at major conferences
- Train FDA reviewers on newly developed safety assessment tools
- Research initiated in the NCTR/FDA Imaging Center
- Research and collaborations expanded in clinical studies
- Guidance documents for the use of new technologies developed in conjunction with the Product Centers as requested by such regulatory groups
- New standards and recommendations developed for use of new technologies for regulatory applications as warranted by the emerging nature of the field and the needs of FDA's regulators

Goal 3: Conduct research and develop strategic technologies to protect the food supply

FDA is responsible for ensuring the safety of foods, food ingredients, and bioengineered foods; defending the food system against terrorist attacks; identifying food-related health hazards; and conducting research to provide a sound basis for regulatory decisions. The scope of the FDA's responsibility encompasses ~ $450 billion in domestic and imported foods or 80% of the nation's food supply. FDA has developed a comprehensive food protection strategy to protect the nation's food supply from both unintentional contamination and deliberate attack. NCTR is integrating its research with other FDA centers and the Office of Regulatory Affairs to develop collaborative projects to develop methods to prevent outbreaks of foodborne illness caused by unintentional and intentional factors. Furthermore, in collaboration with the National Toxicology Program (NTP) and other FDA Centers, NCTR performs studies *in vitro* or *in vivo* to provide dose-response data. These technologies can also be applied to other FDA-regulated products.

Traditional methods for detection and characterization of bacterial contaminants, although time consuming and resource intensive, are well developed and generally accepted worldwide. However, the modern global and agricultural economy has produced a dramatic increase in the numbers, sources, and demands of food products available to the public through advanced agricultural practices and centralization of food distribution networks. The success of the world-wide agribusiness sector also has led to increased opportunity for acts of bioterrorism that can seriously affect public health and/or destroy economies. These realities have raised the need for proven rapid and cost effective detection technologies to protect the food supply. Similarly, unintentional or intentional contamination of the food chain with toxic chemicals in the global economy can dramatically damage health and economies. The need for rapid technologies can be separated into two operational functions:

a) field-rugged test kits capable of general screening for contaminants in numerous matrices at outlet food sources, field laboratories, and ports of entry, and screening for suspect-target organisms during contamination outbreaks at points throughout the food supply chain
b) rapid high-throughput laboratory techniques for both validation of field screens and positive identification/characterization of organisms

Advanced agribusiness practices, including the use of pharmaceuticals, also have led to an increased opportunity for the development and spread of microbial pathogens. Consequently, efficient technologies to identify the microorganisms, trace the spread, and identify effective intervention strategies for highly resistant pathogens are urgently needed.

Objectives and Supporting Strategies for Goal 3:

Objective 3.1 Conduct multidisciplinary research and risk-assessment studies to develop and apply sensitive molecular tools for the rapid detection and characterization of microbiological and chemical agents that compromise food safety and are used in bioterrorism

Strategies for implementation

- Develop and evaluate biological threat agent characteristics in foods by conducting studies on the stability of microbiological and chemical agents in a variety of food matrices
- Evaluate chemical and physical methods for eliminating or inactivating protein toxicants contaminating food contact surfaces
- Develop field-rugged test kits or analytical systems capable of general screening for contaminants in numerous matrices at various outlet food sources, field laboratories, and ports of entry.
- Use new technologies to rapidly identify and assess biological threat agents in food
- Validate and incorporate existing and new threat assessment technologies
- Develop pathogen source-tracking methods and epidemiological monitoring tools to aid in guidance of risk-assessment policy for food safety and biosecurity
- Determine pre-harvest interventions to reduce the spread of pathogenic microorganisms from food animals to humans
- Advance the basic science of isolation, detection, and characterization of foodborne pathogens with further studies to understand the pathogenesis and the genetics of those microorganisms
- Determine vaccine targets using proteomic approaches to identify specific proteins implicated in allowing foodborne pathogenic microorganisms to resist killing by the immune system
- Characterize effects of foodborne toxicants on immune and neuroendocrine systems in the gut

Objective 3.2 Develop rapid, sensitive and cost-effective methods for the identification, quantification, and molecular characterization of potential microbial and chemical contaminants in foods, feed, and other FDA-regulated products

Strategies for implementation

- Participate in FDA research coordinating committee roundtable on rapid detection techniques and application for microbial pathogens
- Identify biomarkers that will characterize and provide detection mechanisms for potential contamination in foods
- Work collaboratively with FDA Product Centers and other federal agencies (e.g., U.S. Department of Agriculture, Environmental Protection Agency, National Institutes of Health, Centers for Disease Control and Prevention, Department of Defense) to study mechanisms of antibiotic resistance, develop markers of foodborne pathogens and, build dose-response models of microbial infection to assess the survival, growth, and infectious components of microbial risk
- Develop rapid, sensitive, and reliable methods for detecting antibiotic resistance

markers of foodborne microorganisms to minimize their emergence, spread, and persistence
- Determine the prevalence and characterization of antimicrobial-resistant bacteria from fish raised in aquaculture facilities and imported seafood and provide data for risk-based inspections
- Determine molecular mechanism of antimicrobial-resistance gene dissemination and emergence in foodborne pathogens isolated from food and veterinary sources
- Develop virulence factor based molecular biological detection methods for microbial source tracking of foodborne pathogens that originate in food animals
- Conduct studies to characterize antimicrobial resistance and virulence determinants in pathogens that are associated with food animals and human infections

Outcomes:

• Bacterial drug-resistance surveillance data provided to FDA reviewers with a listing of emerging drug-resistant strains to aid in mitigating spread of infectious pathogens	FY 2009-2012
• Research provided on limits for Acceptable Daily Intake for antimicrobials in foods vital to development of FDA/CVM Guidance for Industry #159	FY 2009-2012
• Strategies and "value-added" risk-assessment models developed to determine the perils of deliberate contamination of bioterror agents in high-value food matrices (milk, eggs, beef)	FY 2009-2012
• Rapid pathogen and/or chemical source-tracking method and epidemiological monitoring tools tested in prototype to aid in development of risk assessment models	FY 2013
• New methodologies to assess toxin production and intrinsic structural mechanisms of bacterial antibiotic resistance of foodborne pathogens developed for rapid response in an emergency	FY 2009-2013
• Molecular-detection technologies and epidemiological database developed for rapid threat assessment of foodborne emerging pathogens	FY 2009-2011

Measures of Success:

- Comprehensive peer review to validate the food protection research and its Agency impact through SAB oversight
- Partnerships with other agencies, departments, and industry to advance NCTR's research in support of FDA's food protection strategy
- Publications in peer-reviewed journals and presentations at major conferences
- Data provided for the development of a risk-assessment model for food products
- Increased communication in food protection research through NCTR Food Protection Seminar Series

Goal 4: Conduct bioinformatics research and development in support of FDA's regulatory mission

Developing a modern bioinformatics infrastructure for efficient electronic regulatory processes and incorporating new technologies, scientific methodologies, and global business activities is a major FDA initiative anticipated to span the next decade. NCTR will be a principal contributor to FDA's bioinformatics modernization plan through formulating requirements, planning, and development efforts.

NCTR's goal is to extend in-house development of bioinformatics methods and systems to the FDA bioinformatics needs. The goals are two-fold: 1) provide the agency with NCTR expertise in bioinformatics including scientific computing, computational science, and software development; and 2) extend NCTR research outcomes and bioinformatics tools to fulfill FDA's regulatory mission. The goals will ensure that NCTR research outcomes are integrated into FDA's business processes, NCTR linkages with the Product Centers are strengthened, and NCTR capabilities continue to become more diverse, robust, and capable of meeting the future and demanding needs of the FDA.

NCTR contributions to developing the FDA's future bioinformatics infrastructure was formalized with the 2006 formation of the FDA Bioinformatics Board in which NCTR is a member. NCTR has a diverse and experienced group of scientists skilled in bioinformatics to include information technology specialists and software engineers working in a highly integrated environment. NCTR's internal teamwork and external collaborations have led to the success of the MicroArray Quality Control (MAQC) project and ArrayTrack™ software development. NCTR has been successful in efforts to meet the FDA regulatory needs particularly in the area of bioinformatics for high-throughput molecular technologies. These analytical tools produce data for developing pharmacogenomics and nutrigenomics, which are key disciplines for personalized medicine and biomarker identification. NCTR's unique expertise has significantly contributed to the FDA's bioinformatics modernization efforts and has been recognized in the 2008 FDA Science Board report for its leadership in developing, integrating, and providing infrastructure for bioinformatics.

Objectives and Supporting Strategies for Goal 4:

Objective 4.1 Further develop and host bioinformatics infrastructure components, test bed, and production for the electronic regulatory (e-regulatory) submission process

Strategies for implementation

- Host and maintain a bioinformatics capability to translate the e-regulatory submission concept into practice and enhance the Agency's e-regulatory submission capabilities
- Develop bioinformatics infrastructure components extensible to the Agency's infrastructure for e-regulation
- Conduct and participate in the FDA regulatory e-submission pilots
- Lead or participate in the development of standards to establish the basis for an

- Identify user cases to map out best practices for conducting e-submission, facilitating data flow, and review at each stage of the e-submission pipeline

Objective 4.2 Integrate diverse data sources to provide scientific data-intelligence tools to support FDA science and regulation

Strategies for implementation

- Establish software environments to enable collaborative science through integration of analytical data, institutional memory, and knowledge into the scientific discovery process
- Advance the integrated bioinformatics capability and develop novel methodologies to address increasing needs in the fields of systems biology, genomics, pharmacogenomics, predictive toxicology, and personalized nutrition and medicine
- Develop knowledge databases that provide the necessary focused data, knowledge, and analytical tools for areas of regulatory significance.
- Integrate agency-produced research and regulatory test data using Laboratory Information Management Systems (LIMS) into omic databases, ArrayTrack™, SNPTrack, and Janus databases.

Objective 4.3 Develop and transform scientific research for regulatory use via bioinformatics

Strategies for implementation

- Provide subject-matter expertise to the Agency to support the implementation of the science-based bioinformatics infrastructure for analytical tools, data standards, and software development
- Assess existing research products in FDA to identify their potential for regulatory application and establish a bioinformatics strategy to realize their potential
- With prerequisite funding from selected FDA Bioinformatics Board (BIB) sanctioned projects, develop modular, reusable, Web-based software for the FDA bioinformatics infrastructure

Outcomes:

- Regulatory nonclinical e-submission pilot study completed, including establishment of the ToxVision reviewer software server and Janus environment — FY 2009-2012
- Pharmacogenomics e-submission pilot study completed with Pharmacogenomics-capable Janus data structure — FY 2009-2012
- Bioinformatics infrastructure expanded and improved for the FDA Voluntary eXploratory Data Submission — FY 2009-2011
- FDA five-year plan for bioinformatics infrastructure developed in conjunction with the Scientific Computing and Computational science Business Review Board — FY 2009-2010
- Bioinformatics infrastructure for personalized medicine and nutrition completed — FY 2009-2012

- The functionality of ArrayTrack™ expanded to accommodate pharmacogenomics and nutrigenomics data beyond DNA microarrays — FY 2009-2011
- SNPTrack for pharmacogenetics completed — FY 2009-2013
- Database and application servers for the FDA Structured Product Labeling pilot study established — FY 2009-2010
- Nutritional and physical activity databases for research developed — FY 2009-2011

Measures of Success:

- Partnerships with FDA Product Centers, with other agencies and departments, and with industry to advance the e-regulatory process in the Agency
- FDA scientists and reviewers trained for use of ArrayTrack™ and SNPTrack
- Demonstrable contributions to the Janus enterprise software system
- Insufficiencies and inefficiencies of the current e-submission strategies identified through e-submission pilot experience
- Bioinformatics infrastructure that supports the FDA's pharmacogenomics data submission program through both the Voluntary eXploratory Data Submission program and the regulatory submission mechanism
- Integration of NCTR and FDA laboratories data through a commercial Laboratory Information Management Systems (LIMS) with ArrayTrack™, SNPTrack, Janus, and other databases
- Development of software tools and databases for nutritional and physical activity assessments in collaboration with other U.S. government agencies
- Peer-reviewed publications for novel bioinformatics and statistical methodologies to support pharmacogenomics, risk assessment, predictive toxicology, systems biology, and personalized medicine and nutrition

Goal 5: Strengthen and improve scientific and human capital management and expand training and outreach to retain and train scientific experts critical to address FDA's scientific needs

NCTR's ability to efficiently and effectively manage its scientific infrastructure, recruit talented new scientists, and support e-government initiatives mandates the use of modern project and program planning using an integrated budget and performance process linked to the FDA's improved financial performance system. Working collaboratively within FDA and with other government, academic, and industry groups, NCTR will enhance its current management infrastructure and expand the utilization of this Agency-owned laboratory facility.

NCTR scientists support the Agency's regulatory activities by providing technical expertise in the interpretation of data, the development and harmonization of guidelines, and by participating in national and international scientific workgroups and advisory panels.

FDA's success in achieving its mission requires a well-trained scientific staff whose expertise and skills are optimally used to address the complex issues associated with Agency-regulated products. As part of its mission of conducting research, NCTR provides the Agency and the regulatory community with technical expertise, consultation, and training.

NCTR plans to develop a program to train a diverse mix of health researchers. To accomplish this, NCTR will continue its efforts to:

1. Provide mentoring/academic training
2. Provide Arraytrack™ training
3. Provide opportunities for growth and career development through the utilization of new and existing training resources.
4. Provide leadership and development opportunities and training in support of the Center's succession planning efforts

The intent is to provide a well-trained, highly motivated cadre of scientists and regulators fully engaged in the science that is vitally needed by the Agency to promote public health.

Objectives and Supporting Strategies for Goal 5:

Objective 5.1 Establish procedures that improve management efficiencies

Strategies for implementation

- Explore and fully utilize contract options in supporting research objectives
- Tie performance goals and objectives to development of scientific tools that improve human health outcomes that are of value to FDA Product Centers
- Achieve integration of budget and performance information

- Support the (UFMS) Unified Financial Management System
- Enhance communication and efficiency outreach

Objective 5.2 Implement a strategic succession plan to develop and manage human capital

Strategies for implementation

- Creatively use human and technological resources to explore new collaborations and partnerships (leveraging both national and international resources) that will support fundamental research and contribute to the Agency's ability to ensure the availability of safer and more effective products for the consumer
- Use aggressive recruiting and hiring practices to enhance the quality of core research personnel
- Support a fully integrated workplace-diversity plan

Objective 5.3 Establish process to facilitate expert consultation of NCTR scientists within the agency and with outside partners

Strategies for implementation

- Continue support for NCTR scientist attendance at FDA workshops
- Increase participation of Product Center scientists at NCTR scientific reviews
- Increase participation of NCTR scientists in collaborative projects

Objective 5.4 Develop approaches to obtain and optimize utilization of training resources

Strategies for implementation

- Identify opportunities to train a diverse mix of health-science researchers
- Develop collaborations for community-based participatory research for personalizing nutrition, medicine, and healthcare
- Identify opportunities to coordinate with FDA Product Centers in the promotion of collaborative training activities for the FDA Fellowship Program
- Identify opportunities for training provided through the FDA Fellowship Program
- Promote the Science Training and Exchange Professional (STEP) Development Program as part of an Agency-wide sabbatical/fellowship program to cross-train Agency personnel and enhance the understanding of Agency-specific issues through reviewer/researcher scientific exchanges
- Provide state-of-the-art research experience to a cadre of FDA Fellows across the spectrum of NCTR’s integrated research program by allowing the Fellows to participate in studies impacting FDA regulation
- Train undergraduate, pre- and post-doctoral students through mentoring and the use of more formalized training programs such as STEP, the FDA Fellows Program, and other existing training and developmental programs.

Outcomes:

- Joint workshop conducted with a Product Center to foster collaboration — FY 2009
- Contributed to the harmonizing of guidance documents developed for use by FDA Product Centers and the national and international regulatory community — FY 2009-2013
- Expert technical consultation provided to FDA Product Centers, — FY 2009-2013

national and international regulatory community
- Funding provided for STEP program FY 2009
- NCTR's ability to broadcast seminars FDA-wide and ability to participate remotely in FDA seminars established FY 2009-2011
- NCTR employee development and training program established FY 2009-2011

Measures of Success:

- Funding provided for and formalized training offered to 20 technical scientists and post-doctoral researchers annually
- Community-based participatory research program throughout Arkansas expanded
- NCTR 2009-2013 Strategic Plan published

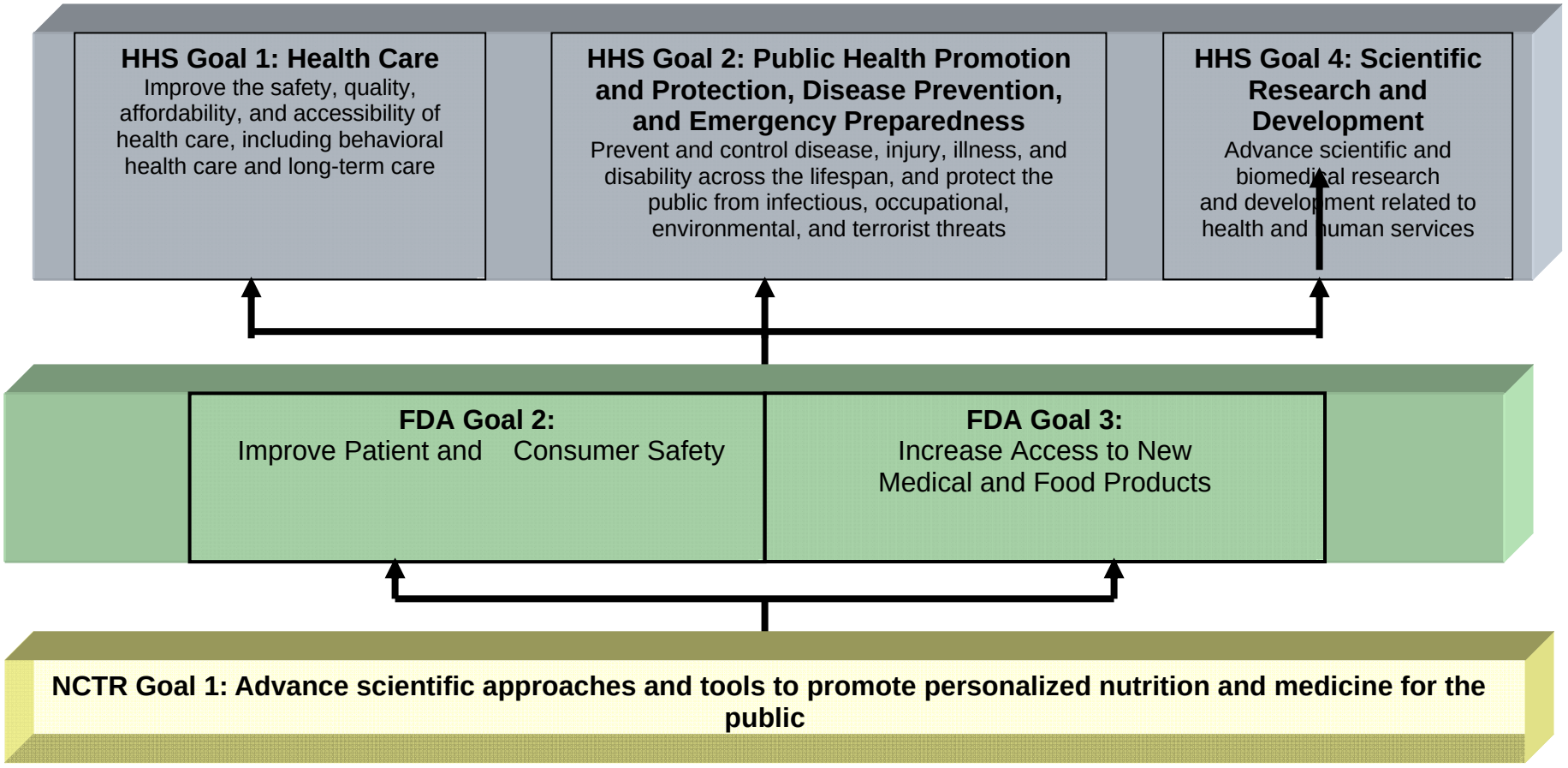
Summary

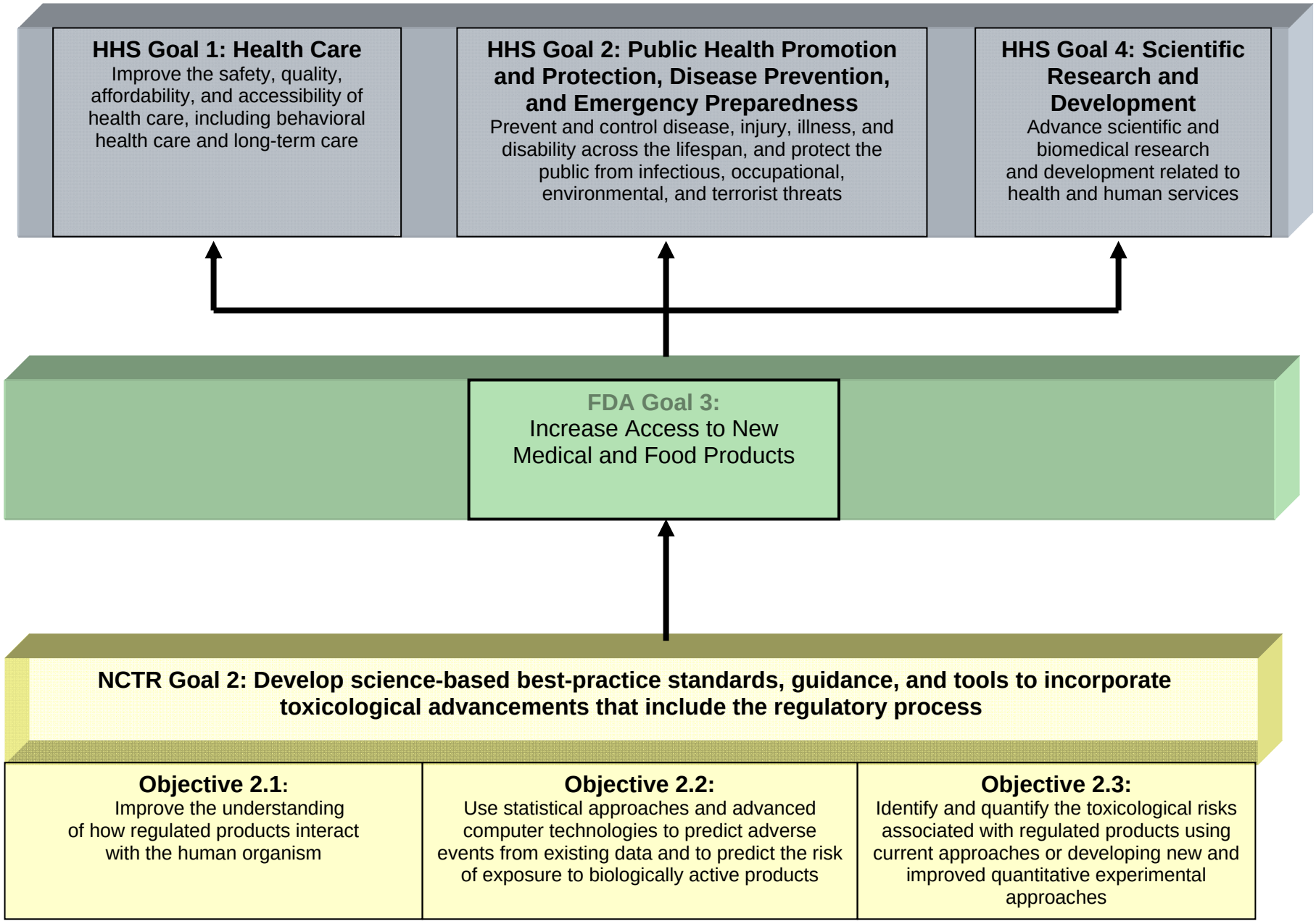
The *NCTR Strategic Plan* is a dynamic roadmap that outlines our commitment to the multidisciplinary translational research essential for anticipating and supporting the FDA's public-health regulatory needs. NCTR research is a vital component of the science-base for the FDA. NCTR science will illuminate the future of the FDA and serve as an effective bridge between discovery and improving and protecting the lives of the public we serve.

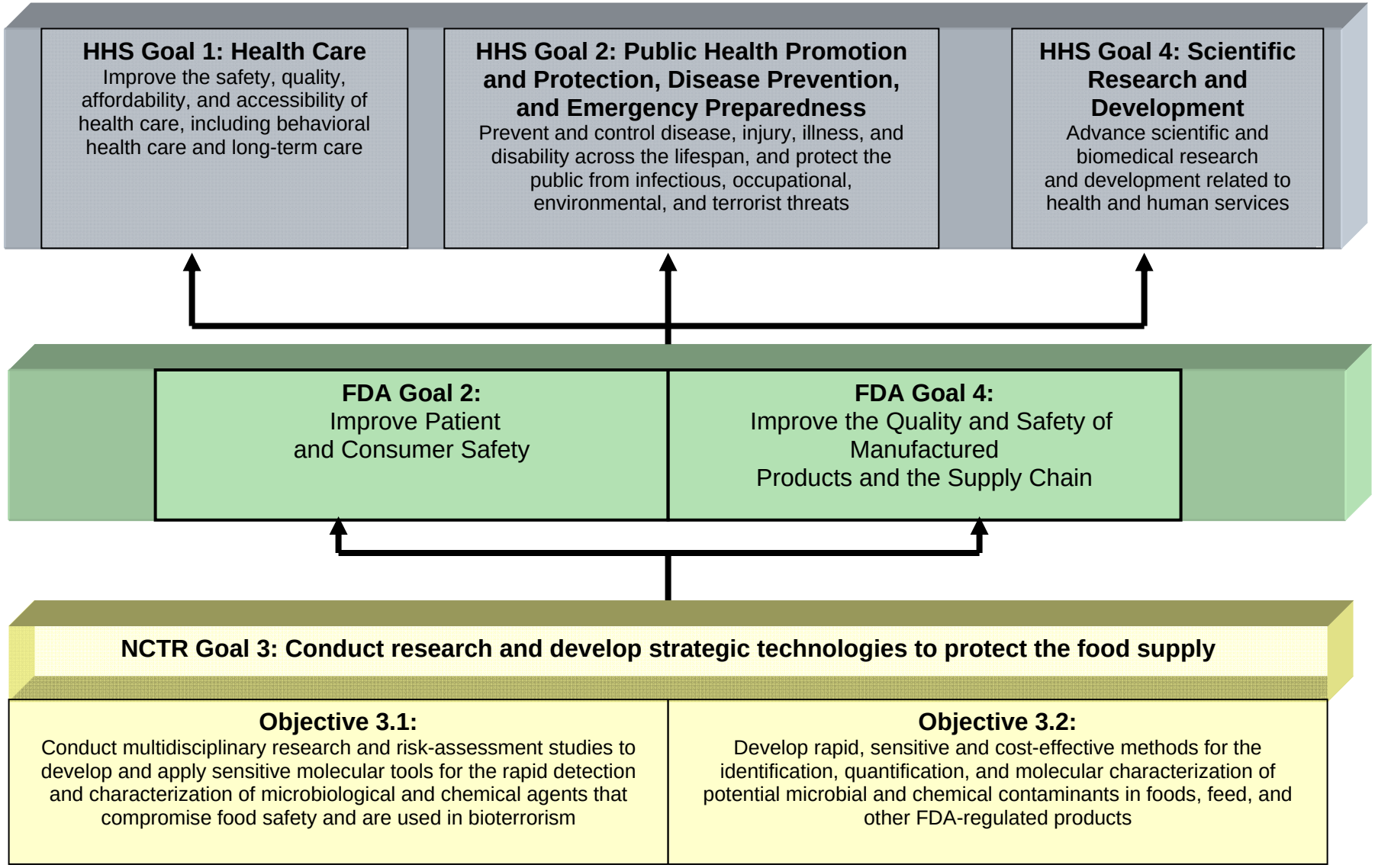
Key Outcomes

- Processes that facilitate expedited development of regulated products to improve personal and public health established
- Access to research knowledge for use by FDA reviewers through advanced technologies increased
- Rapidly accessible research knowledge-database made available for FDA reviewers
- Safety assessment of FDA-regulated compounds improved
- New standards and harmonized guidance for comprehensive assessment of FDA-regulated products developed
- A strengthened scientific basis for food-defense policies and regulatory decisions established
- Risk-assessment decision making improved through a better understanding of mechanisms of toxicity and through new approaches for product safety assessments
- New methodologies and technologies for more accurate regulatory risk evaluation published and adopted by the Agency
- A cadre of cross-trained scientists, reviewers, and FDA Fellows within the Agency established
- NCTR technical expertise optimally used by the FDA Product Centers to support reviews and other activities

Appendix A: Strategic Goal Crosswalk: NCTR–FDA–DHHS




HHS Goal 1: Health Care
Improve the safety, quality, affordability, and accessibility of health care, including behavioral health care and long-term care
HHS Goal 2: Public Health Promotion and Protection, Disease Prevention, and Emergency Preparedness
Prevent and control disease, injury, illness, and disability across the lifespan, and protect the public from infectious, occupational, environmental, and terrorist threats
HHS Goal 4: Scientific Research and Development
Advance scientific and biomedical research and development related to health and human services
FDA Goal 3:
Increase Access to New Medical and Food Products
NCTR Goal 2: Develop science-based best-practice standards, guidance, and tools to incorporate toxicological advancements that include the regulatory process
Objective 2.1:
Improve the understanding of how regulated products interact with the human organism
Objective 2.2:
Use statistical approaches and advanced computer technologies to predict adverse events from existing data and to predict the risk of exposure to biologically active products
Objective 2.3:
Identify and quantify the toxicological risks associated with regulated products using current approaches or developing new and improved quantitative experimental approaches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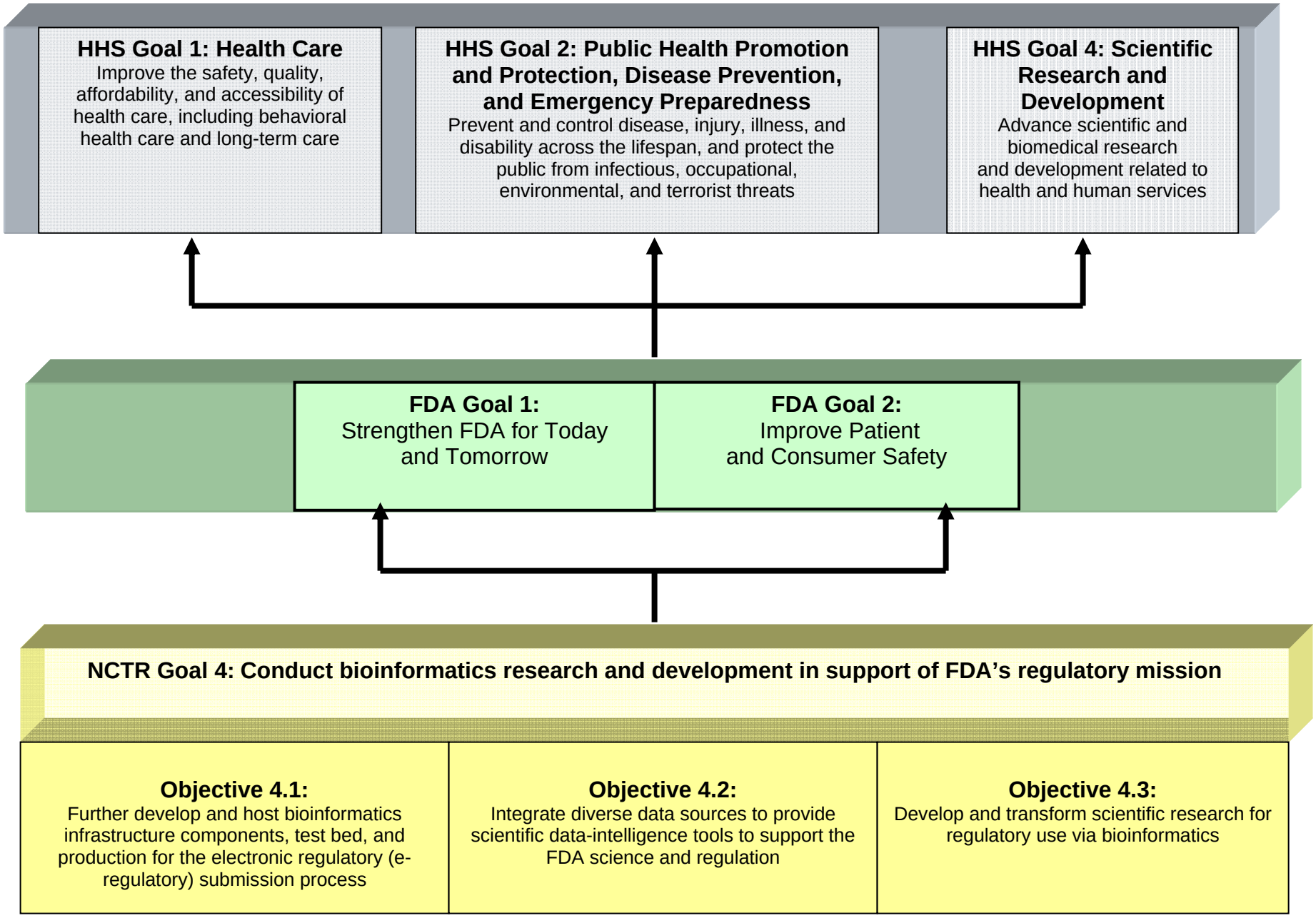
HHS Goal 4: Scientific Research and Development
Advance scientific and biomedical research and development related to health and human services
FDA Goal 2:
Improve Patient and Consumer Safety
FDA Goal 4:
Improve the Quality and Safety of Manufactured Products and the Supply Chain
NCTR Goal 3: Conduct research and develop strategic technologies to protect the food supply
Objective 3.1:
Conduct multidisciplinary research and risk-assessment studies to develop and apply sensitive molecular tools for the rapid detection and characterization of microbiological and chemical agents that compromise food safety and are used in bioterrorism
Objective 3.2:
Develop rapid, sensitive and cost-effective methods for the identification, quantification, and molecular characterization of potential microbial and chemical contaminants in foods, feed, and other FDA-regulated products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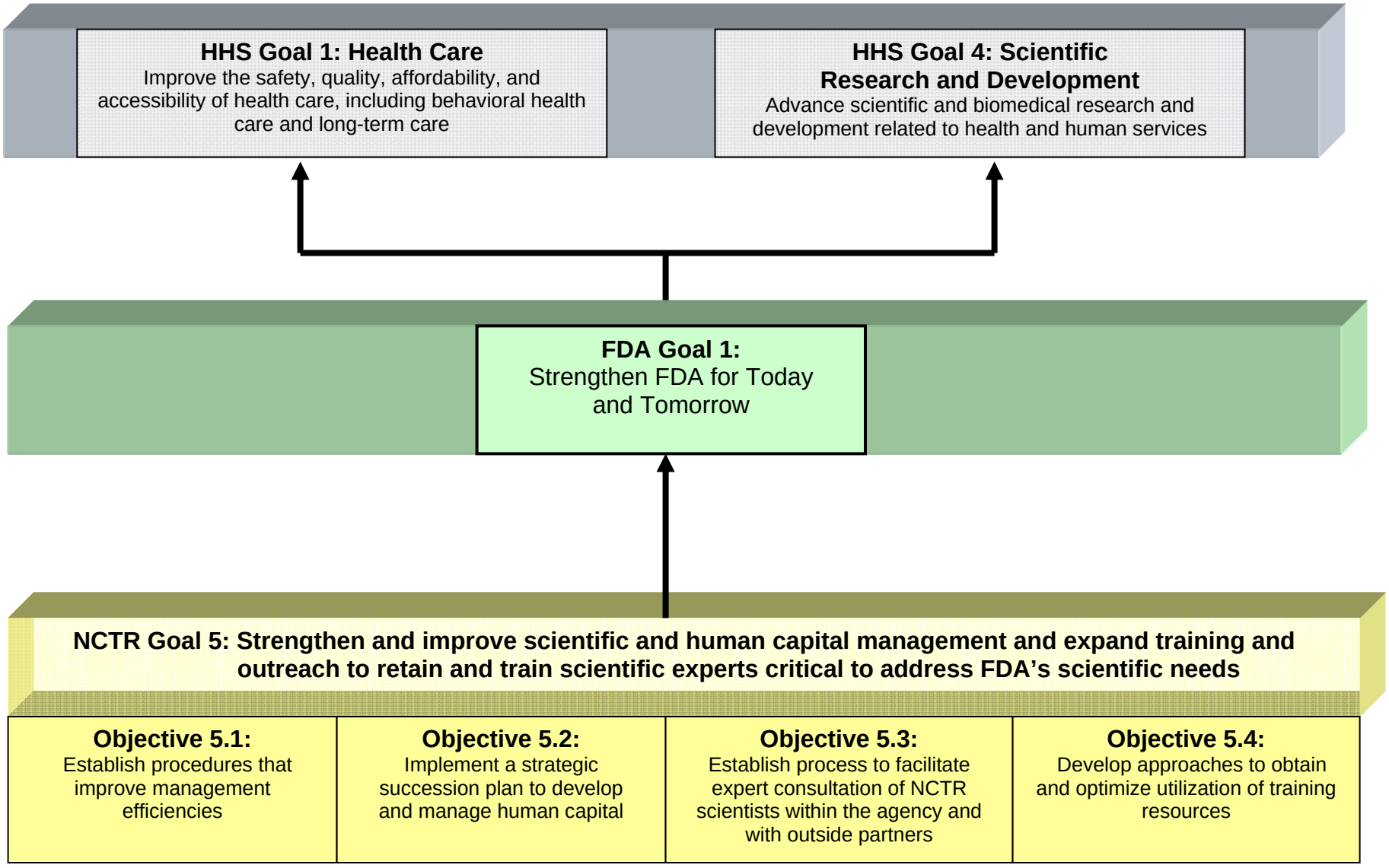
HHS Goal 4: Scientific Research and Development
Advance scientific and biomedical research and development related to health and human services
FDA Goal 1:
Strengthen FDA for Today and Tomorrow
FDA Goal 2:
Improve Patient and Consumer Safety
NCTR Goal 4: Conduct bioinformatics research and development in support of FDA's regulatory mission
Objective 4.1:
Further develop and host bioinformatics infrastructure components, test bed, and production for the electronic regulatory (e-regulatory) submission process
Objective 4.2:
Integrate diverse data sources to provide scientific data-intelligence tools to support the FDA science and regulation
Objective 4.3:
Develop and transform scientific research for regulatory use via bioinformatics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HHS Goal 4: Scientific Research and Development
Advance scientific and biomedical research and development related to health and human services
FDA Goal 1:
Strengthen FDA for Today and Tomorrow
NCTR Goal 5: Strengthen and improve scientific and human capital management and expand training and outreach to retain and train scientific experts critical to address FDA's scientific needs
Objective 5.1:
Establish procedures that improve management efficiencies
Objective 5.2:
Implement a strategic succession plan to develop and manage human capital
Objective 5.3:
Establish process to facilitate expert consultation of NCTR scientists within the agency and with outside partners
Objective 5.4:
Develop approaches to obtain and optimize utilization of training resources

Appendix B: Glossary

Bioactive(s) – often can be characterized as substances that can be isolated chemically that have putative physiological effects, such as cholesterol lowering or change in hormonal status and are often discussed within the realm of prevention of chronic disease (from J. Nutr. 131: 1392S–1395S, 2001)

Bioinformatics – The collection, storage, manipulation, management, and retrieval of biological data.

Biological system – An organism and its design properties, which specify phenotypic outputs given perturbation inputs.

Biomarkers – A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (Biomarkers Definitions Working Group, Clinical Pharmacology & Therapeutics 69:89-95, 2001)

Biometry – The science of collecting and analyzing biologic or health data using statistical methods. Biometry may be used to help learn the possible causes of a cancer or how often a cancer occurs in a certain group of people. Also called biometrics and biostatistics. (from NCI Dictionary of Cancer Terms - http://www.cancer.gov/Templates/db_alpha.aspx?CdrID=514210)

Carcinogen – A substance or chemical agent that perturbs normal cellular processes leading to unscheduled cell division and cancer, or the increased risk of cancer.

Data Model – A conceptual framework for the development of a new or enhanced software application. The purpose of data modeling is to develop an accurate model, which may be shown in a graphical representation such as UML, of the information needs and business processes addressed by a particular application or connected set of operations

Diet – The sum total of all the nourishing materials (food, drink and supplements) consumed by an organism. In humans (and most animals), a proper diet requires certain essential vitamins, minerals, proteins and fats. The balance between starvation and obesity depends on the amount of nourishing materials consumed as fuel and the amount of energy expended.

Dietary Supplements – is a product (other than tobacco) that (i) is intended to supplement the diet, (ii) contains one or more dietary ingredients (including vitamins; minerals; herbs or other botanicals; amino acids; and other substances) or their constituents; (iii) is intended to be taken by mouth as a pill, capsule, tablet, or liquid; and (iv) is labeled on the front panel as being a dietary supplement. Defined by Congress in the Dietary Supplement Health and Education Act (http://www.fda.gov/opacom/laws/dshea.html#sec3), which became law in 1994.

Epigenome – The sum total of all epigenetic modifications of an individual's genome. An individual's phenotype is ultimately a combination of the genotype (all genes and their alleles in the genome) and epigenome (all the chemical modifications of the chromatin).

Expression – A term used to describe the synthesis of mRNA from a gene by the process of transcription. Transcription is achieved with a complex consisting of RNA polymerase II, and several transcription factors all acting on a region of the gene called the promoter. Expression is synonymous with gene activation while lack of expression is equivalent to gene silencing.

Genomics – The high throughput, highly parallel study of all the genes (and gene products - RNA and proteins) as a dynamic system, over time, determining how they interact and influence biological pathways, networks, and physiology, in a global sense.

Genotype – An individual's genetic identity based on the specific set of alleles from maternal and paternal chromosomes. The genotype is not outwardly visible.

Haplotype – A contraction of the phrase "haploid genotype". A specific collection of linked polymorphism (e.g., SNPs, simple tandem repeats, or insertions and deltions) within a cluster of related genes or region of a chromosome.

In silico – is an expression used to mean "performed on computer or via computer simulation"

Metabolomics – Defined as the global analysis of metabolites - - small molecules generated in the process of metabolism - -that represent the sum total of all the metabolic pathways in an organism, with a focus on the identification of each pathway and its role in an organism's function.

Metabolite – Any substance produced by metabolism or by a metabolic process.

Mutagenic – Nanoparticles (nanomaterials) Nanotechnology is the understanding and control of matter at dimensions between approximately 1 and 100 nanometers, where unique phenomena enable novel applications. Nanoparticles and nanomaterials are those materials that have one dimensional aspect (e.g. length, width) between 1 and 100 nm. (National Nanotechnology Initiative; www.nano.gov).

Nutrigenetics – A sub-discipline of nutritional genomics usually referring to the association of a gene variant (see SNP - single nucleotide polymorphism) with an intermediate risk factor (e.g., cholesterol level, or glucose response) that is influenced by a particular nutrients (e.g., saturated fat). Because of genes-genes interactions (see epistasis), nutrigenetics is most informative when viewed in the context of the entire genome.

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Nutrition – A three-step process by which nourishing materials (food, drink and supplements) are ingested, broken down, and utilized in metabolism, to achieve health by sustaining normal cellular activity. As a discipline, nutrition is the study of these processes in the context of health and disease.

Omic – High throughput technologies to analyze various kinds of macromolecules, simultaneously. For example, transcriptomics measures many transcripts, proteomics measures many proteins and metabolomics measures many metabolites.

Oncogene – A gene that can cause cancer or the transformation of normal cells into cancer cells. Normally, an oncogene is an altered version of a normal gene.

Personalized Medicine – delivering the right medicine to the right patient at the right time using evidence-based information.

Personalized Nutrition – optimizing an individual's nutrient intakes throughout the course of life using evidence-based information.

Pharmacogenomics – Pharmacogenetics and pharmacogenomics - The convergence of pharmacology and genetics dealing with genetically determined responses to drugs.

Phenotype – An individual's observable characteristics or traits (e.g., height, weight, hair color or disease) directed by the genotype. The phenotypic can also be affected by epigenetics.

Proteomics – The study of all proteins produced by a cell or organism that are measureable within the cell of origin or body fluids.

Probiotics – defined viable microorganisms, sufficient amounts of which reach the intestine in an active state and thus exert positive health effects.

Single nucleotide polymorphism (SNP) – Common genetic variant consisting of a single nucleotide pair difference between the DNA of the subject or patient and a reference individual. There are about 7 million SNPs in the human genome — some in genes (coding SNPs) and some between genes (noncoding SNPs).

Systems-biology – An approach for studying biological systems that integrates multiple macromolecular species (DNA polymorphisms, RNA, protein, metabolites, etc), bioinformatics, and computational biology. A holistic approach to studying biological systems.