

Advancing Regulatory Science at FDA



U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
U.S. FOOD AND DRUG ADMINISTRATION

Advancing Regulatory Science at FDA

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COVER PHOTO:

DNA test sequencing for scientific research.

Executive Summary



The Food and Drug Administration (FDA) protects and promotes the health and safety of all Americans through enhancing the availability of safe medical products and foods and promoting innovation that addresses unmet medical and public health needs. FDA also protects and promotes the health and safety of animals through assuring the availability of safe animal drug products and food. FDA is a science-based regulatory agency, and a critical component to the success of the nation's public health, health care systems, and economy.

FDA was created in 1906 as one of our nation's principal consumer product protection agencies and is now responsible for assuring the safety of biologics, such as blood products and vaccines, drugs, medical devices, foods, cosmetics, and many other consumer goods. Since 2009, it has also been responsible for regulating the manufacture, marketing, and distribution of tobacco products. In the U.S., FDA-regulated products account for about 25 cents of every dollar spent by American consumers each

year—products that touch the lives of every American every day. FDA is responsible for advancing the public health by helping to speed innovations that make foods safer and make medicines and devices safer and more effective. At the same time, FDA helps consumers and health care providers get the accurate and science-based information they need to make the best possible decisions about their use of medical products and foods for human and non-human animal use. FDA must make decisions based on the best available scientific data and using the best tools and methods available in order to ensure products meet the highest quality standards for consumers, while at the same time fostering and advancing innovation in the products it regulates.

The core responsibility of FDA is to protect consumers by applying the best possible science to its regulatory activities—from pre-market review of efficacy and safety to post-market product surveillance to review of product quality. In the last few years, rapid advances in innovative science have provided new technologies to discover, manufacture and assess novel medical products, and to improve food safety and quality; FDA must both keep pace with and utilize these new scientific advances in order to accomplish its mission to protect and promote the health of our nation.

FDA's Strategic Plan for Regulatory Science

To meet this need, FDA has developed a strategic plan for regulatory science, the



FDA's strategic plan is designed to allow the Agency both to meet today's public health needs and to be fully prepared for the challenges and opportunities of tomorrow.

science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products. This plan identifies eight priority areas of regulatory science where new or enhanced engagement is essential to the continued success of FDA's public health and regulatory mission. The priority areas are:

1. Modernize Toxicology to Enhance Product Safety
2. Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes
3. Support New Approaches to Improve Product Manufacturing and Quality
4. Ensure FDA Readiness to Evaluate Innovative Emerging Technologies
5. Harness Diverse Data through Information Sciences to Improve Health Outcomes
6. Implement a New Prevention-Focused Food Safety System to Protect Public Health
7. Facilitate Development of Medical

- Countermeasures to Protect Against Threats to U.S. and Global Health and Security
8. Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions about Regulated Products

FDA will apply available resources to implement the Strategic Plan for Regulatory Science through management of scientific programs within FDA and engagement of collaborators and partners in industry, academia and government. FDA's Strategic Plan for Regulatory Science is designed to allow the Agency both to meet today's public and animal health needs and to be fully prepared for the challenges and opportunities of tomorrow to help harness revolutions in science that can be translated into products that help make and keep our nation both safe and healthy. [FDA](#)

Introduction



FDA is responsible for assuring the safety of foods, drugs, medical devices, biologics—such as vaccines, blood products, cell and gene therapy products, and tissues—cosmetics, and many other consumer goods, as well as foods and drugs for animals. Since 2009, it has also been responsible for regulating the manufacture, marketing, and distribution of tobacco products. FDA is also responsible for advancing the public health by helping to speed innovations that provide our nation with safe and effective medicines and devices and keep our food supply safe, while helping Americans get the accurate, science-based information they need to use medical products and consume foods to improve and maintain their health.

The complexity of FDA's regulatory and public health portfolio is growing rapidly, in large part due to scientific challenges inherent in evaluating a new generation of products based on quickly evolving science and technology. Layered on this are the realities of an expanding global economy that requires FDA to evaluate and manage risks associated with a vast array and volume of regulatory data, products, and ingredients produced in a multitude of global locations. New drugs, biologics and medical devices are increasingly complex in their development, manufacture, and evaluation. Sophisticated global markets move foods from foreign farms to supermarkets with increasing speed. Finished products may contain a complicated array of ingredients and components, all sourced from shifting global commodities markets and often of uncertain

provenance. The addition of tobacco products to FDA's regulatory responsibilities poses new regulatory challenges in need of new scientific solutions to better protect the public from harm. In addition, improved information technology capacity provides opportunities to harness the substantial data resources both within and external to FDA for regulatory decision-making.

The challenges of modern product development and globalization underscore the critical importance of modernizing and advancing regulatory science to match advances in basic and applied science and technology. Clearly, for scientific advances to realize their full potential for improving public health, FDA must be able to issue clear guidance, play a major role in the improvement of modern product and process

FDA identifies priority areas where new or enhanced investments in regulatory science research capacity will be essential to mission success and to public health and safety.



development tools, and make sound regulatory decisions about risks and benefits of products that increasingly involve new technologies.

To help meet these challenges, FDA has developed this Strategic Plan for Regulatory Science, the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products. This work builds upon the white paper *Advancing Regulatory Science for Public Health*¹ and the *FDA Strategic Priorities*.² In this work, FDA identifies priority areas where new or enhanced investments in regulatory science research capacity will be essential to continued mission success and to public health and safety.

FDA will accomplish this plan by applying its knowledge base, laboratories, scientific computing capabilities, and expertise, while leveraging resources and collaborating with domestic and international partners in government and academia. Where appropriate, FDA will also engage stakeholders from the private sector in this effort. FDA will use this plan to ensure that its regulatory science programs focus on the identified priorities, in combination with Center-specific approaches, but will also revisit these priorities regularly and seek public input to address evolving challenges, opportunities and changes in the science and innovation landscape. [FDA](#)

1. *Advancing Regulatory Science for Public Health* accessible at:

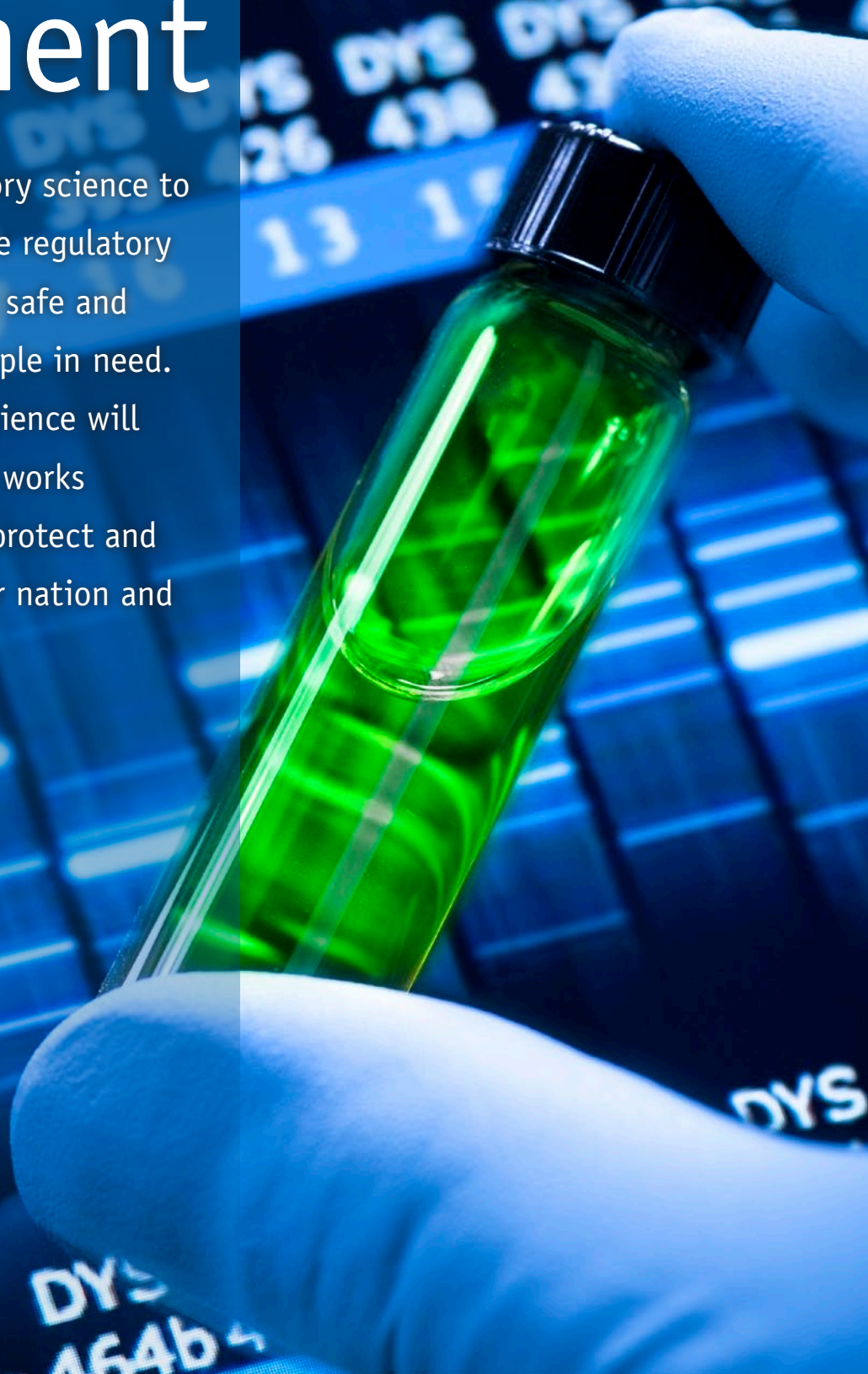
<http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RegulatoryScience/UCM228444.pdf>

2. FDA Strategic Priorities accessible at:

<http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm227527.htm>

Vision Statement

FDA will advance regulatory science to speed innovation, improve regulatory decision-making, and get safe and effective products to people in need. 21st Century regulatory science will be a driving force as FDA works with diverse partners to protect and promote the health of our nation and the global community.





Science Priority Areas

FDA has identified eight priority areas where new or enhanced engagement in regulatory science research is essential to advancing its regulatory mission. These priority areas are not restricted to one product area; rather, they address cross-cutting needs and opportunities that typically extend across several product areas where benefits and engagement from regulatory science successes will enhance product development, evaluation and health outcomes related to multiple products and populations. FDA's strategic plan for regulatory science is critical to the continued success of the Agency in meeting its regulatory mission and facilitating the translation of breakthrough discoveries into innovative, safe and effective products of tomorrow.

1

Modernize Toxicology to Enhance Product Safety

Preclinical testing serves a fundamental role in characterizing the potential risks associated with new FDA-regulated products. However, serious and sometimes rare and unexpected adverse events may be observed in clinical trials or post-approval, suggesting that critical gaps exist in our understanding of the relationship between patient response and preclinical toxicology findings. For example, non-clinical safety assessment is often conducted in normal healthy test systems and tends to be exposure-based; it does not attempt to evaluate the possible risk of rare or idiosyncratic responses that may arise from potential interactions with the presence or progression of disease or the genetic background or other exposures of patients and consumers. Also, in some cases, the true predictive accuracy

of many toxicology models and safety assays remains uncertain and in need of more rigorous validation against actual human and animal adverse event data to define their reliability and possible limitations. For tobacco products, a deeper understanding of the negative effects of tobacco constituents and how best to measure and, wherever possible, reduce those effects is needed to assess public health impact. Finally, the introduction of new measurement technologies and increasing knowledge about toxicity mechanisms and pathways offer important opportunities for advanced computational analyses that can promote the effective translation of non-clinical findings to the clinical setting. FDA can close these gaps and improve preclinical safety predictions by further

investing in three particular areas of regulatory science: the evaluation and development of models and assays that better predict patient response, the identification and evaluation of more reliable biomarkers for monitoring toxicities, side effects, and abnormalities, and the use of computational tools to integrate and draw conclusions from a wide range of preclinical safety data types and sources.

Implementation Strategy

FDA will seek to improve the prediction of product safety and efficacy based on preclinical data by conducting internal and collaborative research to address the following needs:

1. *Develop better models of human adverse response:*

- a) Evaluate and promote the use of cell- and tissue-based assays that more accurately represent human susceptibility to adverse reactions;
- b) Modernize the development and use of animal models that consider the potential influence of disease progression and disease co-morbidities on the emergence of adverse events;

- c) Promote a better understanding of toxicity mechanisms by evaluating safety assessment data at multiple levels of biological organization, including genes, proteins, pathways, and cell/organ function;
- d) Assess and characterize molecular targets and host genetic factors that may be associated with rare and unexpected adverse events (“off-target” drug effects); and
- e) Initiate *in vitro* and *in vivo* studies to identify potential markers of harm associated with exposure to tobacco constituents

2. *Identify and evaluate biomarkers and endpoints that can be used in non-clinical and clinical evaluations:*

- a) Evaluate the accuracy (specificity and sensitivity) with which animal models and cell-based assays correctly predict potential human risk;
- b) Assess concordance between animal and human markers of toxicity and determine how the performance of these markers and their interpretation may vary across different organ systems and human populations; and
- c) Evaluate quantitative imaging (e.g., positron

New Models to Assess Safety of Gene Therapy

1

There are currently numerous clinical trials using a promising new class of cancer therapies based on adenovirus—a variation of a common cold virus that can be engineered to deliver cancer-killing gene therapies. However, rapid clearance of adenovirus by the liver prevents the virus from finding the target cancer cells and, in some cases, may cause liver toxicity. FDA scientists have developed animal models to study how the liver clears adenovirus from circulation and how adenovirus triggers toxic reactions. As a result, they have been able to identify methods to block receptors that the liver uses to clear adenovirus vectors from circulation. They have also identified adenovirus-induced mediators that could potentially be blocked to improve safety. For example, adenovirus injections in rats and mice rapidly induce a toxic mediator that can cause lethal shock. Scientists can block this mediator with a drug, completely protecting the animals from shock.

This will help speed the delivery of safe and effective new products to market, leading to improved health outcomes and reduced risk.



emission tomography, magnetic resonance imaging, computed tomography) and other advanced approaches (e.g., metabolomics) for identifying new biomarkers and predictors of efficacy and safety.

3. Use and develop computational methods and in silico modeling:

- a) Improve the use of chemical Structure-Activity Relationship (SAR) models in the prediction of human risk and integrate this analysis into the review process;
- b) Develop and implement approaches to link chemical structures and substructures to a wide range of information about product safety, disease targets, and toxicity mechanisms;
- c) Develop clinical trial simulation models that can reveal interactions between drug or device effects, patient characteristics, and disease variables influencing outcomes;
- d) Develop computer models of cells, organs, and systems to better predict product safety and efficacy;
- e) Implement computer models that integrate pharmacokinetic, pharmacodynamic, materials science, or mechanistic safety data to predict clinical risk-benefit and confirm post-marketing safety in different patient populations; and
- f) Develop and apply data mining, knowledge building, and data visualization tools to inform computer model development,

clinical risk prediction, and regulatory decision-making.

Public Health Impact

By addressing these needs, FDA will be better able to identify and accurately predict and reduce the magnitude and likelihood of risks associated with products. This, in turn, will help both speed and reduce costs in achieving the delivery of safe and effective new products to market, leading to improved health outcomes and reduced patient risk. By continuing to explore and integrate new tools and approaches in the evaluation of product safety, FDA will be better able to estimate dose ranges, help promote more informed device designs for safe use in clinical trials, and develop and use more sensitive and reliable ways to identify and confirm safety issues at earlier times during the medical product development process. FDA Centers will also be better able to anticipate the risk and nature of product-related adverse events and to understand the mechanisms by which these events occur in specific individuals or subpopulations. Modernizing toxicology and continually improving the ability of non-clinical tests, models, and measurements to predict product safety issues will increase the likelihood that toxicity risks will be identified earlier in product development, assuring patient safety, and mitigating the need to withdraw previously approved products.



Stimulate Innovation in Clinical Evaluations & Personalized Medicine to Improve Product Development and Patient Outcomes

Rapid identification of potential therapeutic targets for medical product development has been facilitated by widely accessible biological information, sophisticated bioinformatics tools to map pathways and build systems biology models, and high throughput screening methods. There has also been significant progress in understanding how genomic variations alter an individual's response to activation or inhibition of these therapeutic targets, enabling potential improvements in the clinical use of existing therapeutics and opening up the possibility of co-developing therapies and tests that can be used to tailor treatment to individual patients (personalized medicine). Indeed, genomic information has already been added to drug labels to identify patients who will most benefit from a drug, identify patients who will be at most risk of an adverse drug reaction, and select the optimal dose for

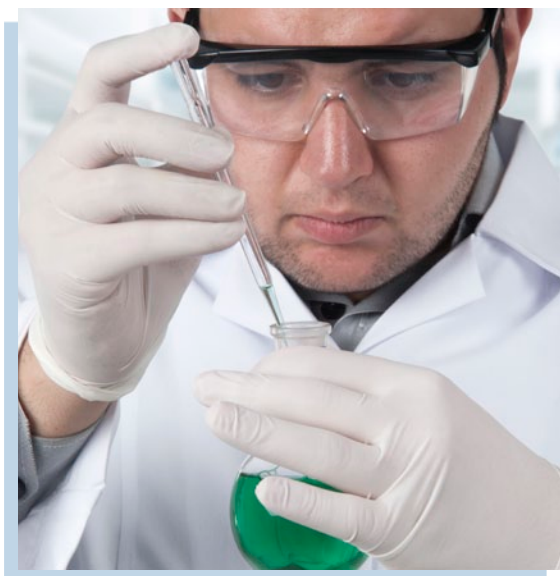
a given patient. Despite this progress, the process of translating new scientific findings into safe and effective use of medical products and optimizing the use of existing products for all populations remains a major challenge. Clinical development programs are lengthy and expensive with uncertain outcomes. There is an imperative to speed efficacious medical products to patients by increasing efforts to reduce the uncertainties in this process.

Clinical development programs for medical products (drugs, biologics, and devices intended to treat disease) are dependent on the availability of tools, such as endpoints predictive of efficacy and toxicity, as well as effective clinical trial design and analysis methods. Central to effective clinical evaluation is the availability of clinically meaningful measures. These often utilize analytical measurements which employ

Companion Diagnostics



Recent biomedical breakthroughs are pushing medicine toward tailored therapeutics, or personalized medicine. Part of this movement means an increase in companion diagnostics—the tests that are used to determine whether a particular therapy may work for a patient. To address this issue, FDA issued the draft guidance *In Vitro Companion Diagnostic Devices* on July 12, 2011, to communicate to industry how FDA defines these devices and what the Agency's regulatory requirements are for them. FDA hopes that by clarifying these topics for industry, we can streamline the process to approve companion diagnostics that accurately steer patients toward targeted therapies so the right patients receive the right drug at the right dose.



FDA's regulatory scientists have a unique ability to facilitate development of knowledge and clinical evaluation tools needed for successful translation of discoveries into viable products.

physiologic, imaging, or genomic endpoints in addition to traditional lab tests. Efforts to assure the accuracy and consistency of analytical measurements while reducing inter-platform and inter-site variability are critical.

Stimulating innovation in the clinical development and evaluation of products requires multiple stakeholders. Addressing challenges in the early phases of drug and biologics discovery, for example, falls within the purview of companies and the biomedical research community. FDA's regulatory scientists, because of their broad and cumulative experience evaluating FDA-regulated product submissions, have a unique ability to facilitate development of knowledge and clinical evaluation tools needed for successful translation of discoveries into viable products.^{3,4} Because the scale of data and effort needed to develop, validate or qualify clinical evaluation tools is enormous, intramural efforts are and should

be supplemented by collaborative projects involving an array of external partners including academia, industry, and global regulatory agencies.

Implementation Strategy

FDA will collaborate with others to help develop the new tools and approaches needed to catalyze the development of personalized medicine and to modernize and advance the science and conduct of clinical trials. Areas of need include:

1. *Develop and refine clinical trial designs, endpoints and analysis methods:*
 - a) Continue to refine clinical trial design and statistical methods of analysis to address issues such as missing data, multiple endpoints, patient enrichment, and adaptive designs;
 - b) Identify and evaluate improved clinical endpoints and related biomarkers for trials in areas where optimal endpoints

3. Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products

<http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm077262.htm>

4. Advancing Regulatory Science for Public Health

<http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm228131.htm>

FDA will collaborate with others to help develop the new tools and approaches needed to catalyze the development of personalized medicine.



are lacking (e.g., efficacy and safety endpoints for osteoarthritis in humans and animals, for gene therapy, for ophthalmic indications, for tumor vaccines, and for stem cell-derived therapies);

- c) Develop novel trial designs and endpoints for special needs (e.g., small trials for orphan indications, designs and endpoints for pediatric trials including neonatal trials);
- d) Continue to refine the use of modeling and simulation in clinical trial design to enhance the effectiveness of clinical studies;
- e) Work with a broad coalition of partners to identify key opportunities for improving the conduct and efficiency of clinical trials; and
- f) Continue development and refinement of tools and approaches for assessing benefit/risk

2. Leverage existing and future clinical trial data:

- a) Develop quantitative models and measures of disease progression; and
- b) Utilize large, pooled clinical trial datasets to identify potential trial endpoints, explore differences in specific populations and subpopulations (e.g., stage of disease, chronic disease states, sex, race and ethnicity, pediatrics and other age groups)

and different subsets of diseases, improve understanding of relationships between clinical parameters and outcomes, and evaluate clinical utility of potential biomarkers (see section 5).

3. Identify and qualify biomarkers and study endpoints:

- a) Facilitate identification and qualification of new and improved biomarkers for safety and efficacy, pharmacodynamic response-dose selection, disease severity, progression and prognosis, and pharmacogenomics (to predict safety and efficacy or guide dosing);
- b) Develop and evaluate novel approaches for biomarker identification, including 'omics, systems biology, and high throughput methods; and
- c) Monitor new developments in personalized medicine as they pertain to regulated medical products.

4. Increase the accuracy and consistency, and reduce inter-platform variability of analytical methods to measure biomarkers:

- a) Reduce inter-platform variability of analytical methods to measure biomarkers through identification of standards and



Facilitating drug and device development for special populations for which safe and effective therapies are very much needed.

- standardized characterization;
- b) Develop evidentiary requirements to demonstrate accuracy and reliability of devices that measure biomarkers using novel or innovative technologies (e.g., whole genome sequencing, new proteomics approaches, image analysis);
 - c) Promote and develop scientific tools to better characterize and standardize measurements which have relied on subjective reading (e.g., computer-assisted diagnostics in imaging, digital pathology devices); and
 - d) Continue participation in collaborative efforts, such as the MicroArray Quality Control Consortium, to evaluate the quality of validation strategies for emerging technologies.

5. *Develop a virtual physiologic patient:*

- a) Encourage the development of computer models that incorporate radiological imaging data of healthy and diseased anatomy from a range of relevant diseases;
- b) Ensure the integration of these models with genomic and other physiological data to promote development of complete

- physiological models and simulations that can be used in the development and testing of medical devices and other medical products; and
- c) Create a library of models so that models validated by FDA are easily accessible to researchers.

Public Health Impact

The public health impact includes the following:

- Facilitate translation of the huge investment in basic sciences by optimizing product development and improving patient and consumer outcomes;
- Further basic knowledge needed to develop human biomarkers of harm from tobacco constituents;
- Maximize individual therapeutic efficacy and minimize harm by identifying predictors of individual outcomes; and
- Facilitate drug and device development for special populations (such as for children, women, and patients with rare or neglected diseases) for which safe and effective therapies are very much needed.

3

Support New Approaches to Improve Product Manufacturing and Quality

Application of novel science and technologies is leading both to innovation in manufacturing and to innovative products that are often complex. In order to foster these innovations, FDA needs to do research—collaborating with industry and academia—to assess how these new technologies affect product safety, efficacy, and quality, and to use the information to inform development of regulatory policy relevant to these innovations.

In addition, analytical technologies are rapidly changing and leading to dramatic improvements in sensitivity, resolution, and precision in the determination of product structure and the detection of contaminants.

Implementation Strategy

FDA will support the application of novel

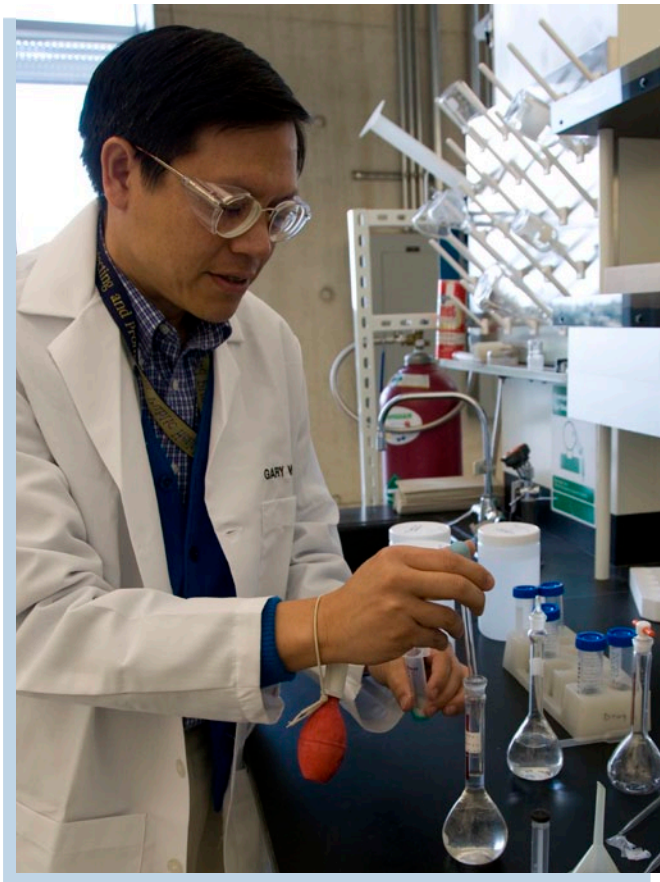
technologies to product development and innovative analytical approaches to improve product manufacturing and quality through active research intramurally and collaboratively with external partners by addressing each of the following needs:

1. *Enable development and evaluation of novel and improved manufacturing methods:*

- a) Investigate the effects of continuous manufacturing (manufacturing using a continuous process, rather than a batch approach) on product quality;
- b) Examine specific novel manufacturing technologies to determine how they impact product failure rates;
- c) Evaluate the role of excipient ingredients and complex dosage forms on product safety, efficacy, and quality; and

Quality by Design

Quality by Design is understanding the manufacturing process and identifying the key steps for obtaining and assuring a pre-defined final product quality. FDA is constantly working to identify ways to improve the manufacturing process to ensure consistent product quality throughout the shelf life as well as to identify when contamination or other production failures may occur. Improved quality by design will also lower product development and manufacturing costs by reducing the likelihood of production failures during a long run and by providing opportunities for continuous improvement. As part of its Quality by Design effort, FDA is now working on three new areas to support increased manufacturing quality. The first is a continuous processing where materials constantly flow in and out of equipment. The second is the use of process analytical technology to monitor and control processes, as opposed to the current method of just testing products. The third is the development of new statistical approaches to detect changes in process or product quality.



Application of novel science and technologies is leading both to innovation in manufacturing and to innovative products that are often complex.

d) Promote two state-of-the-art manufacturing strategies—Process Analytical Technology, and Quality-By-Design approaches—for impact on manufacturers’ ability to maintain consistent quality.

2. Develop new analytical methods:

- a) Investigate feasibility and value of using emerging and improved analytical technologies like Nuclear Magnetic Resonance (NMR), mass spectrometry, or near infrared or Raman spectroscopy for evaluating product quality of pharmaceutical agents, and evaluate whether these technologies should replace existing methods;
- b) Evaluate applicability of various analytic technologies for determination of the “similarity” of biosimilars to their reference products;

c) Perform statistical research to support development and evaluation of new assays and tests needed to assure analytical methods give consistent reproducible results; and

d) Develop improved methods and tools to detect and measure the physical structure, chemical properties, and safety of engineered nanomaterials and complex dosage forms (e.g., transdermal patches, inhalation delivery systems, and targeted drug delivery systems) in FDA-regulated products.

3. Reduce risk of microbial contamination of products:

- a) Develop sensitive, rapid, high-throughput methods to detect, identify, and enumerate microbial contaminants and validate their utility in assessing product sterility;

- b) Develop and evaluate methods for microbial inactivation/removal from pharmaceutical products that are not amenable to conventional methods of sterilization;
- c) Evaluate the impact of specific manufacturing processes on microbial contamination; and
- d) Develop reference materials for use by industry and academia to evaluate and validate novel methods for detecting microbial contamination.

Public Health Impact

Regulatory science research on novel manufacturing methods and on the analysis of products during and after manufacture will facilitate adoption of these methods by industry, thus facilitating and lowering the cost of manufacturing and improving FDA's ability to rapidly evaluate safety, efficacy, and quality of products manufactured by these methods.



Ensure FDA Readiness to Evaluate Innovative Emerging Technologies

We are at a critical moment where advances in science are leading toward fundamental changes in the way medical treatments and diagnostics are being developed and used. Groundbreaking discoveries in complex chemistry and biosynthesis have the promise of yielding new drug candidates, and cutting-edge electronics, nanotechnology and materials science have revolutionized medical

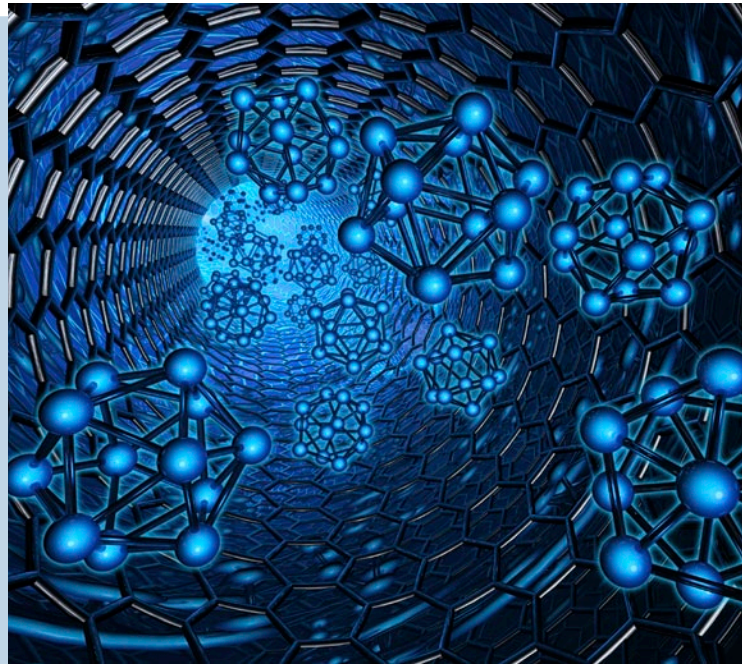
devices. Emerging fields such as gene therapy, cell therapy, tissue engineering, optogenetics, high intensity focused ultrasound, and information technology are also yielding innovative approaches to improve our health. These novel and increasingly complex approaches to health, foods, and medical products present growing challenges to FDA's readiness to evaluate new products. Regulatory

Nanotechnology

As medical products are being revolutionized by cutting-edge technologies like nanotechnology, it is more critical than ever for FDA to fully understand how nanomaterials are being used in these products. FDA has established Nanotechnology Core Centers to provide critically needed equipment and technical staff to conduct product assessment and safety research in support of regulatory decision making. These centers will facilitate investigations on the safety of products that use nanomaterials, establish methods to assess quality and effectiveness of products that use nanomaterials, and identify standards to be incorporated in the preclinical safety assessment of products that contain nanomaterials.



We are at a critical moment where advances in science are leading toward fundamental changes in the way medical treatments and diagnostics will be developed and used.



science must be one step ahead to equip FDA with the necessary tools and methods to reliably assess the safety and efficacy of products derived from these new scientific developments, in order to bring the rewards of discovery safely forward to benefit patients.

Implementation Strategy

FDA will develop necessary expertise and infrastructure to evaluate new and emerging technologies through active research intramurally and collaboratively with external partners to address each of the following needs:

1. Stimulate the development of innovative medical products while concurrently developing novel assessment tools and methodologies:

a) Implement innovation strategies, such as the Center for Devices and Radiological

Health (CDRH)⁵ Innovation Initiative , to facilitate partnerships that create new device development and assessment tools. This initiative explores ways to initiate first-in-human studies earlier in device development, offers an expedited pathway for development, assessment, and approval of important devices, and encourages early conversations with developers to make sure their ideas are translated into technologies that both help patients and are proven safe and effective. Other ongoing initiatives to stimulate innovation include the Center for Veterinary Medicine's (CVM) InnoVation Exploration Team (IVET) to facilitate the discovery of novel approaches and innovative products while maintaining safety, effectiveness, and quality standards; and

b) Encourage promotion of, and participation

5. CDRH Medical Device Innovation Initiative accessible at:

<http://www.fda.gov/AboutFDA/CentersOffices/CDRH/CDRHInnovation/default.htm>



Initial areas under exploration include new brain-computer interfaces, initially coupled with artificial limb technology and the use of wireless technology in healthcare.

in, research and other efforts to increase scientific understanding and help facilitate assessment of data needs for novel regulated products, including those relevant to emerging technologies such as nanotechnology.⁶

2. Develop assessment tools for novel therapies:

- a) Develop new approaches such as *in vitro* and *in vivo* methods to identify measurable characteristics of product safety, quality, and potency when evaluating new therapeutics (e.g., engineered tissues or cell therapy products, including stem cell-derived products, for clinical application in regenerative medicine);
- b) Evaluate and adopt new developments in

the fields of cell biology, developmental biology, and materials science to help us better understand the impact of interactions between living cells and materials used in tissue-engineered medical products, as well as the interaction of cellular products with microenvironments in the patient;

- c) Develop new ways to evaluate gene therapy and antisense therapy products developed during this period of fast-paced scientific progress;
- d) Integrate an understanding of product quality and safety based on novel genomic, proteomic, metabolomic, and other -omic technologies;
- e) Explore the role of wireless and information

6. FDA Nanotechnology Regulatory Science Research accessible at:

<http://www.fda.gov/ScienceResearch/SpecialTopics/Nanotechnology/ucm196697.htm>



FDA will be better equipped to facilitate the translation of groundbreaking new products into effective innovative medical products, while still maintaining the high safety standards Americans depend on.

technologies in new medical therapies and diagnostics; and

- f) Conduct periodic, comprehensive horizon scanning to identify emerging technologies.

3. Assure safe and effective medical innovation:

- a) Develop robust innovation strategies that include reaching out to manufacturers in areas of high public health need with few existing effective interventions and challenging scientific hurdles;
- b) Build upon the clinical research initiatives to ensure rapid and reliable testing of innovative medical products. This may include developing new strategies to detect novel interactions and toxicities posed by novel material and mechanisms of action; and
- c) Help stimulate the development, standardization, and validation of new techniques to assess safety and effectiveness.

4. Enhance readiness for new applications of information technology:

- a) Enhance the collaboration of multidisciplinary scientific expertise within

the Agency when evaluating emerging technology product areas; and

- b) Develop mechanisms to promote cross-disciplinary regulatory science training and research to address scientific gaps and challenges posed by novel products.

Public Health Impact

FDA's efforts will help foster greater predictability in the Agency's regulatory processes, enable innovation, and enhance transparency while protecting the public health. FDA will be better equipped to facilitate the translation of groundbreaking new products into effective innovative medical products, while still maintaining the high safety standards Americans depend on.

5

Harness Diverse Data Through Information Sciences to Improve Health Outcomes

FDA receives a vast amount of information from a variety of sources, including product submissions, adverse event reports, de-identified patient data from health care providers, and results from surveys and basic scientific research. Successful integration and analysis of data from these disparate sources would provide knowledge and insight not possible from any one source alone. A few of the many currently untapped opportunities include: monitoring adverse event trends and disease outbreaks; combining data from multiple clinical trials and postmarket studies as well as preclinical data; evaluating and comparing effectiveness and safety of medical and veterinary products in particular

sub-populations, including sex/gender and race/ethnicity analysis, and ultimately host genomics and/or genomic response data; and large-scale active surveillance for rare events and data- and text-mining for a variety of research purposes.⁷

FDA is in the early stages of constructing the Information Technology (IT) infrastructure necessary for this type of complex data integration, but full realization of the enormous potential in harnessing these diverse data will require extensive improvements to the current FDA IT environment, as well as new analytic approaches and tools. For example, enhancing



FDA receives a vast amount of information from a variety of sources, including product submissions, voluntary adverse event reports, de-identified data from health care providers, and results from surveys and basic scientific research.

7. Additional information on the possibilities of data integration can be found in the PCAST report to the President on Realizing the Full Potential of Health Information Technology to Improve Healthcare for Americans, at <http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-health-it-report.pdf>

PACES Initiative

FDA is currently undertaking projects with enormous potential to unlock the data from product applications reviewed by FDA. By integrating and analyzing these data, FDA will be able to provide industry with new information that can be applied to future product development and potentially save billions of dollars in development costs. One of the programs is the academic Partnership in Applied Comparative Effectiveness Science (PACES) project funded by FDA. PACES facilitates pilot projects to conduct advanced analyses to detect clinical trends to determine which interventions will be most effective for which patients under which specific conditions. This will cut out many of the headaches of trial-and-error to find the right treatment for a particular patient.

FDA's capability to carry out sophisticated data mining activities requires a networking and computational infrastructure that can support an enormous number of simultaneous queries of a large set of indexed data sources.

Within each FDA Center there are ongoing activities that illustrate the range of possibilities and the potential for benefits to public health that would be obtainable. Expansion, coordination, and improvement of the existing IT infrastructure would enhance and augment these ongoing activities.

Implementation Strategy

FDA will develop agency information sciences capability to address the following needs:

1. Enhance information technology

infrastructure development and data mining:

- a) Improve access to large, complex data sets to solve problems faster or to allow solutions of otherwise intractable problems (e.g., multi-dimensional map of *Salmonella*);
- b) Develop secure IT network environment (enclave) for scientific computing and collaborative research with internal (FDA) and external colleagues;
- c) Improve ability to access high speed networking and processing to facilitate transfer and application of computational

functions to large, complex datasets (e.g., cloud computing); and

- d) Identify computational approaches for rapid search and retrieval.

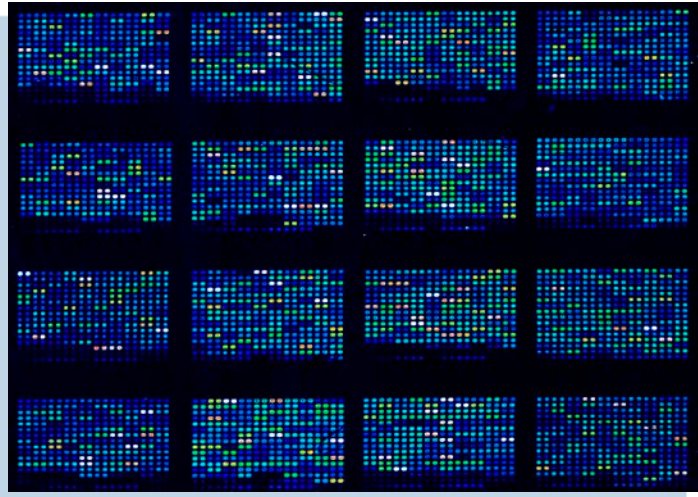
2. Develop and apply simulation models for product life cycles, risk assessment, and other regulatory science uses:

- a) Identify opportunities and develop computer simulation and modeling to streamline data analysis and model biological systems and their responses to agents of concerns, such as toxins, pathogens, electromagnetic energy, and biomaterials; and
- b) Promote novel clinical trial design using simulation, new statistical models, and novel animal models/animal model alternatives.

3. Analyze large scale clinical and preclinical data sets:

- a) Continue to refine methods for analysis of post-market data, including data mining of spontaneous reports and analysis of electronic health records from accessible large healthcare databases;
- b) Continue and expand patient centered outcomes research by compiling datasets converted to standardized format across critical classes of drugs that are entered into

Expansion and improvement of the existing IT infrastructure would enhance and augment these ongoing activities.



the clinical trials repository and Janus;⁸ and c) Provide FDA access to data from a variety of large patient databases, including Sentinel⁹ where FDA is working with multiple partners within government and the private sector. Mini-Sentinel project is an active prototype of the full system.

4. Incorporate knowledge from FDA regulatory files into a database integrating a broad array of data types to facilitate development of predictive toxicology models and model validation (Also see: Section 1)

5. Develop new data sources and innovative analytical methods and approaches:

- a) Lead the development of scientific infrastructure for national and international registries to advance the regulatory science and surveillance of medical products throughout their lifecycle (e.g., International Consortium of Orthopedic Registries - ICOR); and
- b) Advance development of innovative methodological approaches, such as evidence generation, synthesis, and

evaluation throughout device life cycle through the Medical Device Epidemiology Network (MDEpiNet) Initiative.

Public Health Impact

Expansion and improvement of the existing FDA IT infrastructure and application of IT resources to support sophisticated analyses of data will have a number of positive impacts. Access to this data would provide the ability to better predict failure or better design future drugs, future and existing devices, and additional studies. This would increase the efficiency and effectiveness of new products and studies, potentially resulting in better products getting to patients faster. Development and testing of novel methodologies for the synthesis and systematic evaluation of all available evidence will allow comprehensive, up-to-date risk-benefit balance determination at any point of the product life cycle so that FDA can make optimally informed decisions and provide more useful information to practitioners, patients, and industry.

8. Janus is an enterprise initiative to improve FDA's management of structured scientific data about regulated products in support of regulatory decision-making. For more information, please go to <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/ScienceBoardtotheFoodandDrugAdministration/UCM224277.pdf>

9. Sentinel is a national electronic system that will transform FDA's ability to track the safety of drugs, biologics, medical devices, and ultimately all FDA-regulated products once they reach the market. For more information, please go to <http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm>

6

Implement a New Prevention-Focused Food Safety System to Protect Public Health

The recently enacted Food Safety Modernization Act (FSMA), the first major overhaul of our food safety law in over 70 years, will transform FDA's food safety program by providing it with new public health mandates and enhanced tools for ensuring the safety of the food supply in the 21st Century. FSMA emphasizes the concept of preventing problems before they occur and provides new tools to require manufacturers to implement prevention plans. Additionally, FSMA requires FDA to respond quickly and effectively when problems do occur.

Implementation Strategy

FSMA mandates a new approach to FDA's current food safety system, emphasizing prevention and risk-based priority setting and resource allocation to address the challenges of the modern food safety environment. Although prevention is paramount, enhanced response and investigation efforts to

foodborne outbreaks when they occur is also critical. To effectively implement this new food safety mandate, it is imperative that FDA ensures a strong science infrastructure, clearly identifies its research needs, and collaborates with other public health and research agencies in the Federal government, state government agencies, academia, and private industry. Specifically, FDA will focus on the following:

1. Establish and implement centralized planning and performance measurement processes:

- a) Establish and implement Foods Program science/research strategic planning and operational planning processes;
- b) Develop mechanisms to identify and prioritize research needs critical to achieving the Agency's public health and consumer protection goals;
- c) Harmonize microbiological and chemical analytical methods development and validation across the Foods Program to



FSMA mandates a new approach to FDA's current food safety system, emphasizing prevention and risk-based priority setting and resource allocation to address the challenges of the modern food safety environment.

As collaborative global food safety surveillance programs increase, harmonization of standards and validation criteria will allow for greater data sharing and data acceptance between the US and our international trading partners.



Food Pathogens

6

As a regulatory agency tasked to ensure the safety of the nation's food supply, it is imperative that the analytical methods our laboratories employ for surveillance, compliance, and outbreak investigations meet the highest standards of performance. FDA is meeting this challenge through the development of performance standards for all methods to detect microbial pathogens and chemical and radiological contaminants, and to harmonize method validation guidelines for all methods developed and used in our testing laboratories. Currently, guidelines to govern analytical methods designed to detect food-borne microbial pathogens are nearing completion and will cover methods for the detection of food-borne bacterial pathogens (e.g., *Salmonella*, *Listeria*, and *Shigella*) viruses (e.g., Hepatitis A virus, Norovirus) and other pathogens (e.g., *Cyclospora* and *Cryptosporidium*). These guidelines will also address performance evaluation criteria (verification and validation) necessary for the use of commercially-available microbiological diagnostic kits and platforms in FDA regulatory laboratories. At the same time, FDA is also actively collaborating with other government agencies, international partners, and multiple accrediting bodies to achieve a similar consensus on method performance standards and validation criteria. As collaborative global food safety surveillance programs increase, harmonization of standards and validation criteria will allow for greater data sharing and data acceptance between the US and our international trading partners.

The investment in this public health focus will strengthen FDA's ability to prevent the occurrence of future food and feed safety contamination events.



- enhance detection and removal of unsafe contaminants from the Nation's food and feed supply; and
- d) Plan and implement ongoing collaborative activities between science and research elements of programs and Centers and Federal and State partners where appropriate.

2. Improve information sharing internally and externally:

- a) Effectively communicate research plans and results within the Foods Program to Federal and State partners, the public, and other interested stakeholders;
- b) Develop centralized IT infrastructure to collect, analyze, and share foods science/research data with program offices;
- c) Evaluate the impact of publications and presentations on the scientific and regulatory community; and
- d) Improve communication with food importers to provide rapid notification of negative test results

3. Maintain mission critical science capabilities:

- a) Identify and invest in disciplines and specialties that are critical to carrying out the Foods Program mission;
- b) Identify and invest in emerging disciplines, sciences, and technologies to mitigate future risks in food safety (Also see: Section 4); and
- c) Maintain and enhance the science/

technology infrastructure to support day-to-day operations. This will ensure the infrastructure exists at FDA to promptly recognize, evaluate, and ensure effective controls for food and feed safety hazards (microbiological, chemical, and radiological).

4. Cultivate expert institutional knowledge:

- a) Develop integrated Foods Program training requirements and training program for cross-functional scientific staff.

Public Health Impact

An integrated science/research program based on the principles of prevention and risk-based priority setting provides research solutions to support current and evolving FDA regulatory issues and is critical to meet FDA regulatory science priorities outlined in this initiative. The investment in this public health focus will strengthen FDA's ability to prevent the occurrence of future food and feed safety contamination events, and if necessary, quickly respond to microbial and chemical contamination events. This initiative will also allow for greater collaboration and coordination between operating divisions under the umbrella of the Office of Foods (i.e., CFSAN and CVM) and components of ORA and NCTR, and will enable FDA to meet emerging challenges in the food safety arena.

7

Facilitate Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security

Medical countermeasures, or MCMs, are drugs, biologics (including vaccines), devices (including diagnostic tests and personal protective equipment), and other equipment and supplies for response to public health emergencies involving chemical, biological, radiological, or nuclear (CBRN) threat agents or naturally-occurring infectious disease outbreaks. The range of MCMs required to rapidly and effectively respond to these types of public health emergencies is not yet fully developed. Moreover, there is limited capability to rapidly develop a new MCM in response to a new or emerging threat, and only limited capacity to ramp up production of existing MCMs once an event is detected.

An extensive review of the U.S. processes and infrastructure for developing, approving, and stockpiling MCMs, released in August 2010, identified FDA as one of the most critical components of the nation's Public

Health Emergency Medical Countermeasures Enterprise (PHEMCE). Because FDA is responsible for evaluating product safety and efficacy, it has significant understanding of the steps required for successful product development. Harnessing FDA knowledge and expertise in the form of a comprehensive MCM initiative will help establish regulatory pathways based on the most advanced scientific foundations available, accelerate MCM development, and realize the promise of new technologies for faster development and flexible, rapidly scalable manufacture of MCMs.

To attain these goals, in 2010, FDA launched the Medical Countermeasures initiative (MCMi) which consists of three pillars to establish regulatory pathways and accelerate MCM development toward approval: 1) enhancing the regulatory review processes for MCMs; 2) advancing regulatory science for MCM development and evaluation; and



Medical countermeasures, or MCMs, are drugs, biologics devices, and other equipment and supplies for response to public health emergencies.



FDA will facilitate development of safe and effective MCMs through both intramural research and collaboration with external partners.

3) modernizing the legal, regulatory, and policy framework for effective public health response. The second pillar, advancing regulatory science, is critical for realizing the promise of multiyear investments by the nation to develop MCMs, since development of many MCMs is impeded by the lack of key scientific information, animal models, or methods needed to assess their safety or efficacy. In particular, when efficacy studies in humans are unethical or infeasible, studies in animal models¹⁰ will typically be needed to provide the efficacy data required to support approval, licensure, clearance, or emergency authorization. Alternatively, in those cases where no freshly collected human specimens are available for development and validation of diagnostic assays, well-characterized archived specimens or, in some instances, even contrived or simulated specimens, may be used to assess assay performance. To facilitate development of safe and effective MCMs against diseases or conditions caused by CBRN threats or emerging infectious diseases,¹¹ FDA will work closely with the federal government's

PHEMCE partners, as well as academia and industry, to focus its scientific agenda on four overarching areas: develop, characterize and qualify animal models for MCM development; modernize tools to evaluate MCM product safety, efficacy, and quality; develop and qualify biomarkers of diseases or conditions; and enhance emergency communication. In addition, FDA will conduct product needs assessment in collaboration with the clinical community, academia, industry, and Biomedical Advanced Research and Development Authority (BARDA) to identify products that can be delivered efficiently and applied easily without requiring advanced skill or expertise, and furthermore have potential for broadest impact.

Implementation Strategy

In close alignment with priorities identified by the PHEMCE, FDA will facilitate development of safe and effective MCMs through both intramural research and collaboration with external partners (e.g., academia, U.S. government agencies, non-governmental

10. For more on requirements for approval or licensure under these conditions see "The Animal Rule: New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible; Final Rule," 5/31/2002.

11. For the purpose of this paper, "threat agent" will include CBRN threats as well as emerging infectious diseases.

organizations, and industry) to address, for example, the following needs:

1. Develop, characterize, and qualify animal models for MCM development:

- a) Develop and evaluate animal models for the ability to demonstrate a response to the countermeasure that will be predictive for humans, including the ability to extrapolate pharmacokinetic/pharmacodynamic (PK/PD) data from animals to humans to determine appropriate dosing in humans; and
- b) Develop a database of non-clinical efficacy models to support development of biomarkers and endpoints, and inform decision-making on feasibility of certain animal models to support approval or licensure of MCMs (Also see: Section 1).

2. Modernize tools to evaluate MCM product safety, efficacy, and quality:

- a) Partner with the Department of Health and Human Services (HHS) and Department of Defense (DOD) to support and facilitate

development of advanced manufacturing approaches and facilities, including rapid, scalable, platform approaches;

- b) Identify and evaluate methods to improve availability and reuse of personal protective equipment;
- c) Continue to develop electronic data standards and report forms to facilitate rapid assessment of the safety and efficacy of deployed MCMs;
- d) Develop reference materials related to relevant threat agents to facilitate development of preventive vaccines, therapeutics, and detection and diagnostic methods; and
- e) Develop and evaluate high throughput, sensitive, specific, cost-effective methods to detect threat agents, diagnose the disease or condition, and perform broad-based pathogen detection.

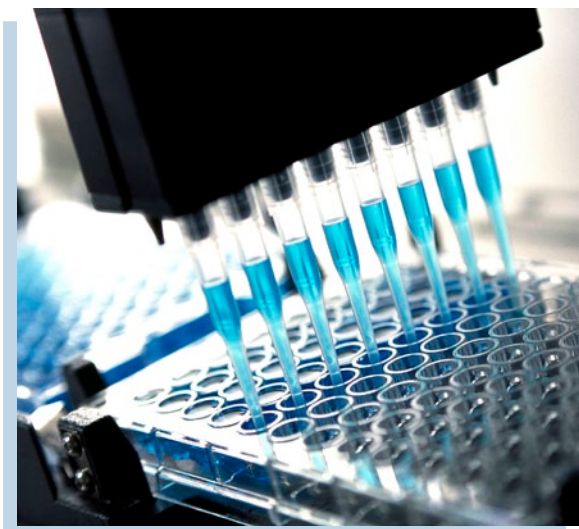
3. Develop and qualify biomarkers of diseases or conditions:

- a) Improve knowledge of natural history of

Vaccines

7

Each year, the influenza vaccine is slightly different due to accumulated genetic changes in circulating influenza viruses. In order to develop a protective vaccine, the strain for the vaccine needs to be matched to the expected strains circulating. Once produced, the manufacturer needs to be able to accurately measure the potency of each strain component in the vaccine, which requires the production of reagent standards, including a strain-specific antiserum. This is typically done by purifying the hemagglutinin (HA) protein from the flu vaccine strain, immunizing sheep with the purified protein, and then using the resulting antisera to analyze the manufactured vaccine. HA purification is time-consuming and often unsuccessful, and can become a rate-limiting step in the final lot release testing on the vaccine strain if the antisera are not available. CBER scientists have shown that they can use recombinant DNA techniques to generate the HA protein in the absence of a virus as an alternative method for preparation of pandemic influenza strain-specific antibody for vaccine potency determination. The resulting antisera from sheep immunized with the recombinant HA have shown identical sensitivity and specificity to those sera obtain from HA purified from the virus.



Advancing regulatory science to support development of MCMs will contribute directly and indirectly to development of safer, better products for other diseases and conditions.

- pathophysiology of human diseases or conditions caused by CBRN agents;
- b) Identify and develop biomarkers that enhance the understanding of the mechanism of action of MCMs, and may provide measures of MCM product efficacy; and
- c) Determine pathogenesis in relevant nonclinical models and evaluate for predictive value to human condition.

4. Enhance emergency communication:

- a) Evaluate past risk and emergency communications to identify and improve the effectiveness of communications in a public health emergency;
- b) Improve quality and health literacy level of FDA communication about FDA-regulated products; and
- c) Enhance FDA's capabilities and develop new strategies to collect, monitor, and track during emergencies real time data on adverse events associated with the use of drug, biologic, and device MCMs.

Public Health Impact

Advancing regulatory science in the areas above will provide enhanced preparedness by establishing more flexible and nimble manufacturing processes and by creating data,

tools, and methods to speed development and evaluation of MCM product safety, efficacy, and quality. Improved scientific data will facilitate development of safer, more efficacious products to respond to threats—should that become necessary—thus mitigating the morbidity and mortality of an attack or outbreak fostering resilience and recovery.

The MCM regulatory science program will bring the nation a step closer to the preparedness and response capabilities articulated in the HHS Public Health Emergency Medical Countermeasures Enterprise Review, where the nation's MCM Enterprise is equipped to respond to any attack or threat, known or unknown.

Ultimately, the output of MCM regulatory science will have substantial implications for improving the health and security of the U.S. population beyond CBRN and emerging infectious disease threats. Advancing regulatory science to support development of MCMs will contribute directly and indirectly to development of safer, better products for other diseases and conditions.

8

Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions about Regulated Products

One way that FDA protects the public from harm and promotes public health is by ensuring easy public access to sound information.¹² This is accomplished by setting and enforcing high standards for product information and quality to ensure that labels are accurate, products truly are what their labels claim, and advertising about these products is clear, truthful, and in no way misleading. FDA also seeks to provide clear information about how to use products to promote health or reduce harm so consumers and health professionals can make informed decisions, and FDA communicates new or emerging situations so Americans have up-to-date information about products on the market.

To enhance the utility of information provided to the public, FDA needs a science-based approach for developing an effective communication strategy, including developing messages, testing how the public understands information, assuring optimal delivery to relevant populations, and assessing the impact of the information on public understanding,

attitudes, and behaviors. A major challenge is adapting FDA’s communications to rapidly evolving technologies that are driving major shifts in how consumers choose to receive and share information.

Implementation Strategy

To facilitate the translation of science-based regulatory decisions and information into public health gains, FDA must strengthen social and behavioral sciences in the areas of understanding and reaching diverse audiences, ensuring audience comprehension, and evaluating the effectiveness of communications in changing behaviors related to the use of regulated products. FDA scientists are working internally or collaboratively to address the following needs:

1. *Know the audience:*
 - a) Improve understanding of how the multitude of factors related to the individual (e.g., age, sex, race/ethnicity, zliteracy, motivation, skills) and the information



FDA needs a science-based approach for developing an effective communication strategy.

12. Hamburg MA, Sharfstein JM. The FDA as a Public Health Agency. N Engl J Med 2009 Jun 11;360(24):2493-5

provided on or with products (e.g., wording, placement, required vs. voluntary) impact decision makers' responses to product, label, and agency-provided information.

2. Reach the audience:

- a) Improve understanding of information channels and identify the most effective methods of delivering information to an intended audience, including audiences with diverse backgrounds;
- b) Identify the most effective methods to inform tobacco retailers about FDA's regulatory and enforcement authorities; and
- c) Expand understanding of how online media promote and advertise FDA-regulated products.

3. Ensure audience understanding:

- a) Enhance understanding of how message format and content affect consumers' and health professionals' attitudes about regulated products;
- b) Assess how consumer perceptions of risks associated with FDA-regulated products are affected by product claims;
- c) Improve methods to convey complex scientific and quantitative information about product risks and benefits (e.g., quantitative risk information, clinical trial results, toxicology data) to consumers and professionals; and

- d) Understand how exposure to non-target messages (e.g., promotional offers, distractions in TV ads) affects consumers' understanding of product information.

4. Evaluate the effectiveness of communication about regulated products:

- a) Develop methods to identify and track public understanding, perceptions, and attitudes towards product-related information;
- b) Describe the impact of format and content on behaviors related to product use or misuse, including prescribing practices;
- c) Develop methods to rapidly assess public understanding and attitudes about recalls and other time-sensitive FDA messages to make timely adjustments to the information and/or channels when appropriate; and
- d) Determine the impact of FDA-regulated direct-to-consumer advertising on reporting of adverse events associated with product use.

Public Health Impact:

Strengthening social and behavioral sciences will allow FDA to better equip American consumers and health professionals with the information they need to make sound decisions about using, prescribing and dispensing products. This has the potential to decrease preventable adverse events related to FDA-regulated products. [FDA](#)

Tobacco Regulation

8

Under the Family Smoking Prevention and Tobacco Control Act (P.L. No: 111-31), FDA is responsible for the regulation of the manufacture, distribution, and marketing of tobacco products. Following an experimental study that tested 18,000 adult smokers and susceptible youth on the relative effectiveness of various graphic health warnings, in June 2011 FDA launched new graphic health warning labels for cigarettes, marking a significant advance in communicating the dangers of smoking. These new labels mark the first change in cigarette warnings in more than twenty-five years. The nine new labels warn of risks such as addiction, cancer, and lung disease, and will be required on all new cigarette packages beginning September 2012.

Importance of a Strong Regulatory Science Culture and Infrastructure

Implementation Strategies for the Strategic Plan for Regulatory Science



This report has outlined a number of priority areas where FDA believes advances in the underlying regulatory science will catalyze innovation in regulatory review as well as product and methods development. Each scientific emphasis area presented in this plan represents opportunities to drive a new and important research agenda using a variety of means, from enhancing the FDA internal research program to participation in consortium models.

By identifying key scientific challenges and implementation plans within each priority area, FDA is providing a guide for its regulatory science efforts and a focal point for research and development activities beyond the walls of the Agency. It should be noted that while FDA is a science-based agency that does and will continue to directly support regulatory science research, it is not primarily a funding agency. FDA is, however, an agency that has scientific staff spanning diverse disciplines from food science to engineering to medicine, who are making important contributions to the biomedical, tobacco, toxicology, and foods science research enterprises. The sections below briefly describe

some of the potential avenues for fostering a strong regulatory science culture, improving the scientific infrastructure, and promoting and engaging in the regulatory science research agenda laid out in this plan.

Partnerships with Government Agencies

Currently FDA is actively collaborating with several government agencies and departments to provide guidance, co-sponsor, collaborate, or partner to promote regulatory science programs. These relationships include the formation of an NIH-FDA leadership council, which launched its first Regulatory Science Requests for Applications (RFA) under which four regulatory research programs

are currently being supported, as well as ongoing and active participation in the design, development and approval of projects that are part of the NIH Biomarkers Consortium.

FDA is continuing to explore expansion of efforts with NIH as well as new efforts with other agencies to promote and support regulatory science research and development. A critical component of the FDA science strategic plan will be implemented through enhanced collaborations between FDA and other agencies, both to leverage funding for supporting outside research but as importantly to establish new, collaborative, intramural research projects where expertise from each agency can be brought to bear on regulatory science research projects.

Staff Scientific Training and Professional Development

In addition to the proactive regulatory science efforts outlined in this plan, it is essential to maintain the capacity and in-house scientific and technical expertise needed both to evaluate increasingly complex and innovative products and technologies and to respond rapidly and effectively to public health emergencies. A strong in-house science base and a network of collaborations is necessary to help support FDA's success in addressing these public health challenges, and FDA is supporting various mechanisms where staff have opportunities to increase their knowledge and skills, thereby strengthening the Agency's science base. FDA staff training and professional development is enhanced by participation in scientific and professional meetings and conferences

where experts present their most current research and through collaborations and relationships, both formal and informal, with academic institutions that provide FDA with access to cutting edge science through courses, workshops, and seminars. Academic collaborations also support faculty coming to FDA to impart their knowledge, in addition to FDA staff participating in academic activities and initiatives to bring knowledge back to the Agency. Additionally, every year the Commissioner's Fellowship Program brings talented young scientists with cutting edge experience in academia, industry, and government to FDA every year to work with FDA scientists and learn about regulatory science and review.

Direct Funding Mechanisms

The FDA product Centers and Offices, such as the Office of Critical Path Programs within the Office of the Commissioner are currently engaged in direct support of relevant scientific programs in the form of grants, cooperative agreements, or contracts. These programs supply both research support and in many cases collaborative engagement with and guidance from scientists across the Agency. Recent examples include RFAs to fund cooperative agreements for regulatory science programs in the areas of reproductive toxicology and biomarker qualification, and for a pilot program to potentially support a regional academic collaboration with a Center for Excellence in Regulatory Science and Innovation (CERSI) to support regulatory science research, training, scientific exchanges, and professional development. Moving forward, FDA will continue to engage

A critical component of the FDA science strategic plan will be implemented through enhanced collaborations between FDA and other agencies.

selectively in direct funding mechanisms to seed important areas of science noted in this strategic plan. FDA's limited funds, however, will generally need to be targeted for initial pilots or start up funds that will be used to leverage resources from other sources, such as other government agencies, industry through consortium models, or philanthropy. FDA will continue to identify key areas for investments through issuance of competitive solicitations and will work to partner, in particular with the NIH, to directly support as much of the regulatory science agenda as feasible.

Public-Private Partnerships

Public-Private Partnership (PPP) models are a key component of the implementation strategy for FDA regulatory science. PPPs are one mechanism that can be used to leverage FDA resources by working collaboratively with both public and private partners, to achieve our mission as well as that of the partners. PPPs may take many forms and can range widely in size and scope. In addition, PPPs provide a means to leverage funds from academic institutions, FDA, other government agencies, and industry to support regulatory science priority areas as defined in this plan.

FDA can collaborate with partners from a wide range of other organizations including,

but not limited to, patient advocacy groups, professional societies, charitable foundations, industry members, trade organizations, and academic institutions. FDA PPPs can be designed around the strategic priorities set forth herein and constructed in ways that advance the regulatory science research efforts of FDA in an efficient and cost-effective manner. Because these partnerships will be science-driven, aimed at advancing regulatory science, and structured to uphold the principles of transparency, fairness, inclusiveness, scientific rigor, and compliance with Federal laws and FDA policy, they are a valuable tool to achieving the Agency's mission of advancing regulatory science. Currently FDA is engaged in several PPPs including the Clinical Trials Transformation Initiative and MDEpiNet Initiative.

One unique vehicle for establishment of PPPs is the Reagan-Udall Foundation (RUF), a non-profit foundation established by Congress for the purpose of advancing the regulatory science that FDA needs to accomplish its mission. RUF was designed to be a vehicle for bringing an array of resources and perspectives to bear on high priority FDA regulatory science projects. RUF can create consortia of patient groups, industry, academia, and FDA scientists to design and implement regulatory science research.

FDA can collaborate with partners from a wide range of other organizations including, but not limited to, patient advocacy groups, professional societies, charitable foundations, industry members, trade organizations, and academic institutions.

Moving Forward

The headlines are replete with examples of the critical scientific role the Agency plays in addressing crises, such as contaminated heparin, melamine in pet food, outbreaks of food-borne illness, and questions about vaccine safety, seafood safety, or readiness for pandemic influenza. A strong FDA science infrastructure provides the essential foundation for ensuring scientific excellence and integrity in all of our regulatory and public health decisions and activities. Successful engagement of other scientific communities in academia, industry, and government will be essential to attainment of FDA goals. FDA scientists must work in an environment that fosters creative thinking, promotes scientific multidisciplinary interaction and collaboration, offers opportunities for learning, ensures both scientific excellence and integrity, and provides access to state-of-the-art laboratory and computer technologies. The Agency will develop creative ways to use technology to expand opportunities for training and

collaboration, leverage external expertise and infrastructure through collaborative mechanisms to broaden the range of research possibilities, and provide joint training opportunities with external partners. It will also maximize the impact of regulatory science investments by publishing in peer-reviewed scientific and medical journals and communicating research findings to the public by using Internet tools, such as its existing web site at www.fda.gov as well as some of the newer Web 2.0 tools available, to the maximum extent possible. In addition, to ensure the regulatory science remains up to date, FDA will periodically use the FDA Science Board and other outside scientific expertise to aid in identifying and prioritizing research efforts and to provide input on the relevance, quality, and productivity of the Agency's regulatory science programs. A successful regulatory science program will translate key findings into FDA guidance and communications, both informal and formal, that reflect the latest scientific understanding as it relates to regulatory policy and decision making. [FDA](#)

Conclusion

Advances in science and technology are moving forward rapidly and have created unprecedented challenges and opportunities in U.S. and global health. FDA plays a critical role in protecting and promoting the nation's health and regulates industries that are among the most successful and innovative in the world. Critical responsibilities across the products FDA regulates require application of the best available science to keep pace with these advances and make decisions and take actions that both support innovation and protect and promote the public health.

The FDA Strategic Plan for Regulatory Science identifies critical priority areas and activities where new or enhanced engagement in regulatory science research is essential to continued mission success. Successful implementation of this regulatory science plan, including engagement with diverse stakeholders, will allow the Agency to fulfill its regulatory mission today while also being prepared for the new challenges of tomorrow.

Glossary



BARDA	Biomedical Advanced Research and Development Authority
CBER	Center for Biologics Evaluation and Research
CBRN	Chemical, Biological, Radiological, or Nuclear
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CERSI	Center for Excellence in Regulatory Science and Innovation
CFSAN	Center for Food Safety and Applied Nutrition
CTP	Center for Tobacco Products
CVM	Center for Veterinary Medicine
DARPA	Defense Advanced Research Projects Agency
DOD	Department of Defense
FDA	Food and Drug Administration
FSMA	Food Safety Modernization Act
HA	Hemagglutinin
HHS	Department of Health and Human Services
ICOR	International Consortium of Orthopedic Registries
IT	Information Technology
IVET	Innovation Exploration Team
MedEpiNet	Medical Device Epidemiology Network
MCMi	Medical Countermeasures Initiative
NCTR	National Center for Toxicological Research
NIH	National Institutes of Health
NIST	National Institute for Standards and Technology
NMR	Nuclear Magnetic Resonance
OC	Office of the Commissioner
ORA	Office of Regulatory Affairs
PACES	Partnership in Applied Comparative Effectiveness Science
PCAST	President's Council of Advisors on Science and Technology
PHEMCE	Public Health Emergency Medical Countermeasures Enterprise
Pk/PD	Pharmacokinetic/Pharmacodynamic
PPP	Public-Private Partnerships
RFA	Requests for Applications
RUF	Reagan-Udall Foundation
SAR	Structure-Activity Relationship
U.S.	United States