FY 2013-2014

Regulatory Science Progress Report

In Fulfillment of Requirements Under the Food and Drug Administration Safety and Innovation Act, Section 1124

Food and Drug Administration
Department of Health and Human Services

i. Executive Summary

In fiscal year (FY) 2013 and FY 2014, Food and Drug Administration (FDA) scientists, working both internally and through public-private partnerships with researchers from the academic community, industry, other government agencies, and patient advocacy groups, carried out a comprehensive program of regulatory science activities to realize the intent of the Food and Drug Administration Safety and Innovation Act (FDASIA)[1] and ensure that Americans had increased access to safe and effective drugs and biologics, including generic drugs and biosimilars, and medical devices. As described in more than 1,500 publications in peer-reviewed scientific journals, this program sought to lay the foundation for increased rigor and consistency in regulatory decisions and to speed the translation of discoveries in a variety of emerging scientific areas to viable medical products. FDA's regulatory science research program priorities are laid out in its *Strategic Plan for Regulatory Science*, published in August 2011. Following the program priorities bulleted below this report summarizes significant FY 2013 and FY 2014 FDA research accomplishments related to medical product development. The report satisfies the first of two years of performance reporting requirements described in Section 1124 of FDASIA. [2]

- *Modernize toxicology to enhance product safety*. FDA researchers extended and refined computational models that help regulators predict toxic effects based on structural information. They also continued to develop innovative animal models— for example, a mouse with an engrafted human immune system to help predict patients' adverse immune responses to new drugs and biologics.
- *Stimulate innovation in clinical evaluations and personalized medicine to improve product development and patient outcomes*. Statisticians studied alternative clinical endpoints that could be used to streamline approval of drugs to treat chronic diseases. For example, pathologic complete response, an endpoint found to be highly correlated with survival in women treated for breast cancer, was used to support approval of a drug for preoperative treatment of this disease.
- *Support new approaches to improve product manufacturing and quality.* FDA biologists used systematic approaches to identify key manufacturing parameters that govern the quality of biologics. For example, researchers identified fermentation conditions critical for the anticancer activity of targeted monoclonal antibodies.
- *Ensure FDA readiness to evaluate new and emerging technologies.* FDA developed a computational "Virtual Family" of anatomically correct models now being used to investigate how various devices interact with the body.

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[1] Public Law 112-144, July 9, 2012 available at http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf

[2] The second reporting requirement covers the fiscal years 2015 and 2016.

- *Harness diverse data through information sciences to improve health outcomes*. FDA developed mechanistically-based pharmacokinetic models that make use of diverse clinical and nonclinical data and have been used to support approval of a number of drugs for use in children.
- *Facilitate development of medical countermeasures to protect against threats to U.S. and global health and security*. FDA researchers are devising new ways to produce more effective vaccines to protect against a range of potential biologic threats.
- *Strengthen social and behavioral science to help consumers and professionals make informed decisions about regulated products.* FDA conducted two studies to determine if comparative claims in direct-to-consumer ads influenced perceptions and recall of drug information.

In advancing regulatory science, FDA has been in close communication with diverse stakeholders through well over 100 public workshops and meetings where new scientific advances and their implications for product development, and the regulatory questions they raise, can be discussed by experts from diverse backgrounds.

FDA has adopted and integrated the new scientific knowledge into regulatory practice through advanced scientific training of its staff and the issuance of guidance to industry. FDA scientists have developed more than 150 guidances on scientific topics that underlie medical product development. These documents provide recommendations to drug developers that can streamline development in areas where science has created new regulatory challenges – for example, guidance on how to determine bioequivalence for new classes of complex drug products, and how to integrate new clinical tools such as biomarkers into the regulatory process.

FDA's regulatory mission is increasingly based on information sciences, and in FY 2013 and 2014 the Agency undertook multiple initiatives to realize its commitment to the development, implementation, and maintenance of a comprehensive data standards program to facilitate the efficient and effective review of regulatory submissions. FDA developed and implemented innovative software systems to help reviewers identify data deficiencies and allow them to spend less time organizing and verifying the quality and consistency of regulatory submission data, thus freeing them to address critical questions related to efficacy and safety. The new EmpiricaSignal program to detect drug-related adverse events in the post-market setting is now used by over 400 reviewers at FDA. Finally, the Agency has enhanced its research capacity by making key investments in advanced technologies that will allow its vibrant research community to stay on the cutting edge of regulatory science.

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Introduction

FDASIA, signed into law on July 9, 2012, 1) provided for initial or renewed user fee funding programs for prescription drugs, medical devices, generic drugs, and biosimilars; 2) gave FDA new authorities to address the challenges posed by an increasingly global drug supply chain; 3) emphasized the need to increase stakeholder engagement; and 4) intended to spur innovation in medical product development by enabling the Agency and its stakeholders to realize the promise of recent unprecedented scientific advances—in genomics, computational sciences, imaging technologies, and many other critical areas—for medical product development. Section 1124 of FDASIA required FDA to develop a Strategy and Implementation Plan for Advancing Regulatory Science for Medical Products[3] (Strategy and Implementation Plan). Issued in July 2013, this document identified regulatory science gaps related to FDA's priorities and described how these gaps were to be addressed and how scientific advances would be integrated into the regulatory process. The law further required that for FY 2014 and FY 2016, the annual performance reports covering FDA's regulatory activities under the user fee agreements would be accompanied by a report on the progress made with respect to (1) advancing the regulatory science priorities and resolving the gaps identified in the Strategy and Implementation Plan, (2) integrating and adopting advances in regulatory science, and (3) advancing the regulatory science goals outlined in Prescription Drug User Fee Act (PDUFA) commitment letter, the Generic Drug User Fee Amendments of 2012(GDUFA) commitment letter, the Biosimilar User Fee Act (BsUFA) commitment letter, and the Medical Device User Fee Amendments of 2012(MDUFA) commitment letter. Because the user fee agreements were initiated in FY 2013, this report covers progress in fiscal years 2013 and 2014.[4]

Advancing Regulatory Science Priorities and Resolving Gaps

Continually guided by consultation with scientific and clinical experts, patient advocate groups and other stakeholders such as the drug development community at large (e.g., through workshops and advisory committees), and often leveraging the expertise and resources of investigators in industry and academia, FDA's program of regulatory science research has grown considerably in the past decade. In the past two years, FDA researchers in the three medical product centers (Center for Drug Evaluation and Research, CDER; Center for Biologics Evaluation and Research, CBER; and Center for Devices and Radiological Health, CDRH) have authored or coauthored over 1,500 scientific publications in addition to presenting hundreds of scientific presentations and posters at scientific meetings, seminars, advisory committee meetings, workshops, and international regulatory gatherings. FDA's research has addressed

[3] www.fda.gov/downloads/scienceresearch/specialtopics/regulatoryscience/ucm268225.pdf
[4] In a few instances, accomplishments (e.g., guidances and journal articles) are listed with publication dates that fall a few weeks beyond October 2014.

critical areas of need such as increasing the efficiency of clinical trials, improving communications with consumers and prescribers, advancing vaccine development, applying *in silico* modeling to inform regulatory decision making, enhancing product quality, and facilitating biomarker development to guide treatment and further personalized medicine.

Collaborative interactions with external partners and the variety of mechanisms employed have increased in FY 2013and FY 2014. New public private partnerships have been established, including the Medical Device Innovation Consortium,[5] and the Kidney Health Initiative.[6] FDA's medical product centers are now engaged in 20 public private partnerships that are addressing focused research areas, including data standards for specific disease areas, models of disease progression for Alzheimer's, genetic markers of the risk of drug-induced adverse events, and the safety of anesthetics in children. FDA continues to promote regulatory science education and academic collaboration through its Centers of Excellence in Regulatory Science and Innovation (CERSI)[7] program. Two new CERSI programs were established in 2014 at the University of California, San Francisco/Stanford and Johns Hopkins University. The Reagan-Udall Foundation,[8] in collaboration with the FDA and the Alzheimer's Association,[9] signed a memorandum of understanding to establish a Fellowship within FDA's Division of Neurology Products to identify opportunities for collaboration with patient groups, academic researchers, and pharmaceutical manufacturers to advance the development of treatments for Alzheimer's and other dementias, while also establishing the Innovation in Medical Evidence Development and Surveillance (IMEDS) Program[10] to advance the science and tools necessary to support post-market evidence generation on regulated products and to facilitate utilization of a robust secondary electronic healthcare data platform for generating better evidence on regulated products in the post-market settings. Finally, the Sentinel Initiative,[11] through successful completion of the Mini-Sentinel Pilot Program, has leveraged electronic health care records from over 178 million patients across 18 data partners to support hundreds of queries related to post-marketing surveillance of the safety of medical products.

Adopting Advances in Regulatory Science

Integration of new regulatory science into the regulatory process also has progressed through a number of mechanisms. For example, reviewers have access to dedicated course offerings, symposia dedicated to specific issues in regulatory science, intramural journal clubs and seminars, and conferences where FDA scientists present their work to the research community.

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[5] www.deviceconsortium.org
[6] www.asn-online.org/khi/
[7] www.fda.gov/scienceresearch/specialtopics/regulatoryscience/ucm301667.htm
[8] www.reaganudall.org/
[9] www.alz.org/
[10] http://www.reaganudall.org/our-work/safety-and-better-evidence/imeds-program/
[11] www.fda.gov/safety/fdassentinelinitiative/default.htm

The medical product centers have organized or co-sponsored over 50 workshops or public meetings, engaging stakeholders and external experts in discussions related to advancing regulatory science and strategies for integrating the new science into the regulatory process. Similarly, through the advisory committee process, FDA seeks scientific recommendations from top experts on broad scientific questions critical to applying the best science to regulatory decision making.

Equally important for the integration of scientific advances into the regulatory scheme to improve medical product development is the issuing of guidances to sponsors. These documents represent current FDA thinking on specific scientific approaches and standards to guide the development and assessment of safety, efficacy and quality of medical products. In FY 2013 and FY 2014 the medical product centers issued over 100 draft or final guidance documents, in addition to 129 product-specific bioequivalence guidances. Topics addressed included new antimicrobial development programs, a new pathway for the development and assessment of drugs to treat breast cancer, scientific recommendations for the validation of biomarkers, integration of pharmacogenomics information into drug evaluation, enrichment strategies for clinical trials, and recommendations for increasing data standardization in medical product applications. Guidance topics in the area of medical devices included design considerations for clinical trials, the evaluation of gender-specific data, and devices which contained wireless technology.

Organization of This Report

Each of the first four sections of this report is tailored to one of the user fee agreements and presents examples of key scientific accomplishments by FDA scientists and collaborators that address questions fundamental to realizing the law's intent—expediting the development and review of safe and effective drug products (PDUFA), generic drugs (GDUFA), biosimilars (BsUFA), and medical devices (MDUFA). Also presented are selected examples of how FDA adopts and incorporates regulatory science in areas relevant to each of the goals, e.g., advisory committee meetings, training activities, and developing and issuing scientific guidance documents. Because of the large number of outcomes related to advancing and adopting regulatory science noted above, a detailed description and explanation of each one's impact is beyond the scope of this progress report. Thus, each section provides illustrative examples.

The final section of this report is a more complete compilation of cross-cutting regulatory science accomplishments applicable to one or more of the user fee agreements in such areas as public-private partnerships, guidance, training, and improving FDA's research infrastructure. Congress requested that FDA develop "clear and measureable metrics" for reporting on our progress in regulatory science, and as requested these metrics were submitted in 2013 as part of the *Strategy and Implementation Plan for Advancing Regulatory Science for Medical Products* required by FDASIA. These metrics are used throughout to organize the reporting of regulatory science activities.

I. Advancing Regulatory Science to Promote the Development of Safe and Effective Drug Products under PDUFA

The fifth reauthorization of PDUFA ensured that FDA will continue to receive a source of stable and consistent funding during FY 2013-2017, one that allows the Agency to fulfill its mission to protect and promote public health by helping to bring to market critically needed new drugs for patients. Under this agreement, FDA identified activities it would undertake to meet specific scientific challenges in the areas of clinical trial endpoint assessment tools, biomarkers and pharmacogenomics, statistical inference across multiple studies (meta-analyses), and development of drugs for rare diseases. These and many other areas of emerging science are contributing to a rapid transformation of the regulatory science of drug development that is the impetus for this progress report. For example, FDA received 13 applications containing genomic data in 2013, and the volume of pharmacogenomic data encountered by reviewers is expected to expand significantly in the coming years. Continued advances in the science and technology of biomarker development have required careful scientific evaluation of these new tools— FDA's Drug Development Tools program is one way in which FDA is refining its regulatory practice to realize the potential of biomarkers to transform drug development. Another driver of change in regulatory science is the increased contribution by the discipline of statistics—new and innovative clinical trial designs (e.g., adaptive designs) and growing recognition of the utility of Bayesian approaches to evaluate data are active areas of research at the Agency by statisticians, who like many FDA scientists, may conduct targeted research to a specific area of regulatory need in addition to review activities.

Also driving a transformation of regulatory science are continued advances in information technology. The sheer volume of electronic information that reviewers must analyze makes continued investment in advanced software systems a critical priority for a variety of reasons, not least of which is that the comprehensive displays of the data they can provide enable reviewers to identify issues more quickly in the review process. With advances in computational science, modeling and simulation have become critical to regulatory decision making; for example, pharmacometric modeling approaches are increasingly used by reviewers to understand data deficiencies and how available information can be rationally extrapolated to populations for whom data is lacking.

Clearly rapid changes in the complexity and sophistication of product design, coupled with advances in manufacturing technology and global sourcing present continued regulatory science challenges for ensuring product quality. Advances in analytical technologies have also allowed FDA scientists to shed new light on quality issues related to old products; for example, for heparin, FDA developed new analytical methods and quality standards that bring added certainty about the quality of product entering the market and contribute to the assessment of generic versions of this complex molecule.

This section contains examples of key regulatory science research accomplishments contributing to the development of safe and effective, high quality drugs, organizing them according to the priority areas in FDA's *Strategic Plan for Regulatory Science*. Examples of how FDA has adopted and incorporated scientific advances into its regulatory processes through guidances, advisory committee meetings, scientific training and other activities are also presented. A fuller representation of FDA's regulatory science efforts, including crosscutting developments in computational systems, research infrastructure, and data standards, is provided in Section V of this report.

i. Addressing Scientific Gaps

1. Intramural Research

> We will provide a description of the most important regulatory science accomplishments as they relate to identified gaps. We will include explanations of (1) their significance for advancing regulatory science, (2) their impact on regulatory decision-making, and (3) their impact on the scientific community as evidenced by relevant peer-reviewed publications and other publicly available disseminations of the findings.
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> Strategy and Implementation Plan, p. 44.

The accomplishments below and in following sections are organized according to priority areas in FDA's Strategic Plan for Advancing Regulatory Science that apply to medical products. They are as follows:

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, is not applicable to medical product development[12]
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

[12] Priority 6 does not apply to medical products and is therefore not referenced in this report.

Significant Accomplishments by FDA Researchers (FY 2013-2014)

Accomplishment	Significance
Modernize Toxicology to Enhance Product Safety	
Improved prediction of genotoxicity. *In silico* approaches based on quantitative structure-activity relationship (QSAR) modeling are vital to the evaluation of the toxicity of new molecular entities. Using data on hundreds of molecular entities, FDA researchers constructed a mutagenicity model that covered a wider range of molecular species and showed better sensitivity than models currently in wide use. Stavitskaya L, et al., Society of Toxicology 53rd Annual Meeting, (MS in preparation).	A new predictive model developed by FDA researchers is designed to improve assessment of the genotoxic potential of new compounds.
The relationship of diet to the safety of drugs to treat diabetics. Glucagon-like Peptide-1 (GLP-1) drugs are currently used to treat type-2 diabetes, but these drugs are associated with increased risks of pancreatitis and pancreatic ductal metaplasia. FDA researchers investigated the effects of diet and GLP-1-based drugs on the exocrine pancreas in a mouse model of insulin resistance and found evidence that that pancreatic toxicity caused by these drugs can be exacerbated by a high fat diet. Rouse, R., Xu, L., Stewart, S., & Zhang, J. (2014). High fat diet and GLP-1 drugs induce pancreatic injury in mice. *Toxicology and applied pharmacology*, 276(2), 104-114.	This study may help provide a basis for more informed and safer use of a class of drugs used to treat diabetes.
Ensuring the safety of anesthetics. The requirement for prolonged anesthetic exposure in certain individuals, (e.g., newborns subject to long-term surgery) has raised concerns about neurotoxicity. Researchers at FDA's National Center for Toxilogical Research have devised imaging techniques based on positive emission tomography that use specific protein or small molecule probes to achieve cellular resolution in vivo of the effects of anesthetics on the developing brain. Zhang, X., Paule, M. G., Wang, C., & Slikker, W. (2013). Application of microPET imaging approaches in the study of pediatric anesthetic-induced neuronal toxicity. *Journal of Applied Toxicology,* 33(9), 861-868..	Imaging methods developed by FDA that are based on positron emission tomography promise to improve our ability to assess the potential neurotoxic effects of anesthetic exposure.
Identifying better biomarkers of drug-induced pancreatic injury. FDA researchers evaluated circulating microRNAs as potential biomarkers of drug-induced exocrine pancreatic injury in a variety of animal models and found that they were potentially more informative than currently used serum markers. Goodwin et al., Biomarkers. 2014 Sept;19(6):517-29.	Injury to the pancreas has been linked to the use of over 100 drugs, but is often under-reported or misdiagnosed. Improved biomarkers for this drug-induced adverse event will support more effective safety evaluations of new drugs.
Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes	
Improving and streamlining the clinical evaluation of new drugs. The thorough QT study, which involves measurement of the QT interval on an	The thorough QT study lacks specificity, and sole reliance on

Accomplishment	Significance
electrocardiogram, is required for the approval of all new NMEs based on the finding several decades ago that drugs which prolonged the QT interval were more likely to cause fatal arrhythmias. FDA researchers have identified additional ECG parameters that reflect a drug's effect on specific ion channels in heart muscle cells and could provide greater specificity than the QT interval for predicting the risks of fatal arrhythmias Johannesen, L., Vicente, J., Gray, R. A., Galeotti, L., Loring, Z., Garnett, C. E., ... & Strauss, D. G. (2013). Improving the assessment of heart toxicity for all new drugs through translational regulatory science. *Clinical Pharmacology & Therapeutics*.95: 501-508.	its results could lead to the abandonment of many promising drug candidates. The study provides a potential basis for more accurate prediction of the cardiotoxic risks of new drug candidates.
More rapid evaluation of potential breast cancer therapies. FDA researchers found a strong correlation between pathologic complete response (an endpoint based on pathologic findings after neoadjuvant chemotherapy that can be assessed early in cancer trials) and event-free survival in breast cancer patients. Statistical analysis of the strength of the association provided justification for further consideration of this endpoint as part an accelerated approval process for new cancer therapies. Cortazar, P., Zhang, L., Untch, M., Mehta, K., Costantino, J. P., Wolmark, N., ... & von Minckwitz, G. (2014). Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. *The Lancet*. Volume 384, Issue 9938, 164 – 172.	FDA issued guidance on the use of pathologic complete response in neoadjuvant trials for breast cancer, and granted accelerated approval to Perjeta (pertuzumab) for certain patients with HER-2-positive breast cancer, based on the use of pathologic complete response as an endpoint.
Making clinical trials more informative. Adaptive clinical trial designs, which allow changes to trial conduct based on interim data (e.g., adjusting numbers of patients assigned to a given treatment, adding or removing treatment arms) have the potential to streamline clinical evaluation of new drugs, for example by increasing trial efficiency and statistical power. Since 2012, FDA statisticians have published a number of collaborative research articles on adaptive designs and have successfully applied sound scientific methods based on current innovative research to advise sponsors on trial design and make recommendations regarding sponsor's applications (references below). One active research area involves adaptive selection of dose(s) or patient subsets, with enrichment based on the clinical endpoint of interest or biomarkers. Goede V, Fischer K, et al, Obinutuzumab plus chlorambucilin in patients with CLL and coexisting conditions. NEJM, 2014; 370:1101-10 Fox J, Master Protocol for squamous cell lung cancer readies for launch. Nature Biotechnology, 2014; 32,116-118.	The adaptive designs being investigated by FDA researchers have been proposed in drug applications submitted by pharmaceutical sponsors.
An alternative statistical approach that could support improved decision making in clinical trials. FDA researchers worked as part of the safety sub-team of the Drug Information Association Bayesian Scientific Working Group to evaluate challenges associated with designing and analyzing safety trials and provided an overview of specific Bayesian statistical methods that have potential to increase	Most medical product development studies may have limited ability to detect important differences in safety endpoints, especially when

Accomplishment	Significance
the efficiency and safety trials of products. Price, K. L., Amy Xia, H., Lakshminarayanan, M., Madigan, D., Manner, D., Scott, J., ... & Thompson, L. (2014). Bayesian methods for design and analysis of safety trials. *Pharmaceutical statistics*, 13(1), 13-24.	addressing rare adverse events and evaluating safety across several trials whose data quality varies. The probabilistic interpretation the Bayesian approach offers holds great promise for improving safety assessment.
Accelerating evaluation of drugs to treat hepatitis C. FDA researchers assessed data from a set of clinical trials of chronic hepatitis C therapies and found that an earlier endpoint (sustained virologic response at week 12) was as informative in terms of clinical outcome as sustained virologic response at week 12. Chen, J., Florian, J., Carter, W., Fleischer, R. D., Hammerstrom, T. S., Jadhav, P. R., ... & Birnkrant, D. (2013). Earlier sustained virologic response end points for regulatory approval and dose selection of hepatitis C therapies. *Gastroenterology,* 144(7), 1450-1455.	The work confirmed that an earlier endpoint could be used for regulatory approval of therapies to treat hepatitis C and thus made it feasible to streamline clinical evaluations of drugs to treat this chronic disease.
Personalizing an enzyme replacement therapy. Although enzyme replacement therapy (ERT) is a highly effective therapy, CRIM-negative (CN) infantile Pompe disease (IPD) patients typically mount a strong immune response which abrogates the efficacy of ERT, resulting in clinical decline and death. FDA researchers demonstrated that immune tolerance induction prevents or diminishes the development of antibody titers, resulting in a better clinical outcome compared to CN IPD patients treated with ERT monotherapy. Banu Banugaria, S. G., Prater, S. N., Patel, T. T., DeArmey, S. M., Milleson, C., Sheets, K. B., ... & Kishnani, P. S. (2013). Algorithm for the early diagnosis and treatment of patients with cross reactive immunologic material-negative classic infantile Pompe disease: a step towards improving the efficacy of ERT. *PloS one*, 8(6), e67052.	The research suggests that induction of immune tolerance is safe and improves efficacy of enzyme replacement therapy for a severe inherited disease.
Providing critical information to improve gene therapy. Gene therapy researchers widely believed that adenovirus vectors used the blood clotting protein factor X to bind to the liver, which removed them from circulation. This suggested that preventing factor X binding would improve the ability of vectors to reach their targets. FDA researchers showed that the vectors use factor X as a shield from immune system attack; thus, removing factor X would render vectors vulnerable to attack and removal from the body. Xu, Z., Qiu, Q., Tian, J., Smith, J.S., Conenello, G.M., Morita, T., & Byrnes, A.P. (2013). Coagulation factor X shields adenovirus type 5 from attack by natural antibodies and complement. *Nature medicine*, 19(4), 452-457.	This discovery represents a major change in thinking about the design of adenovirus gene therapy vectors that will enhance the ability of researchers to develop treatments using them.
New approaches for developing vaccines to retroviruses. Although live attenuated viruses are among our most potent and effective vaccines, there are potential safety problems in using immunodeficiency virus (HIV) as an immunogen. In rhesus macaques FDA researchers used the live attenuated rubella vaccine strain RA27/3 as a vector to express SIV and HIV vaccine antigens and found that these vectors were highly immunogenic. Virnik, K et al., Live attenuated rubella vectors expressing SIV and HIV vaccine antigens replicate and elicit durable immune responses in rhesus macaques	The study established that Rubella vectors can serve as a vaccine platform for safe delivery and expression of SIV and HIV antigens and that these vectors, tested in a primate model, may be useful for developing vaccines against a variety of viruses.

Accomplishment	Significance
Retrovirology 2013, 10:99.	
Support New Approaches to Improve Product Manufacturing and Quality	
Ensuring the quality of a treatment for radiation poisoning. Using spectroscopic and thermogravimetric approaches, FDA researchers performed stability studies of Prussian Blue, a compound that can bind tightly to radioactive isotopes of thallium and cesium. Prussian Blue is an FDA-approved medical countermeasure for treatment of affected individuals in the event of a nuclear attack or "dirty bomb, " events which could lead to radiation poisoning with isotopes of thallium or cesium. FDA investigators determined that rate at which critical quality attributes of this compound, such as bound water content and thallium binding capacity, decreased over time. Mohammad A, Faustino PJ, Khan MA, Yang Y Long-term stability study of Prussian blue - a quality assessment of water content and thallium binding. *Int J Pharm* 2014 Dec 30;477(1-2):12.2-7	The study determined the rate at which Prussian Blue would lose effectiveness under warehouse conditions and thus furnished a rational basis for determining how often to replace national stockpiles of approved medical countermeasure.
Controlling the quality of monoclonal antibodies used to treat cancer and other chronic diseases. Biologics pose formidable challenges in the area of product quality and manufacturing. FDA researchers used systematic approaches to identify key production parameters affecting glycosylation of monoclonal antibodies (one example of such a parameter would be the temperature at which cells expressing the antibody are grown). Glycosylation is the addition of various sugar residues to proteins, and the pattern of glycosylation of a protein therapeutic is often a critical determinant of its effectiveness (e.g., glycosylation may affect the antitumor activity of targeted antibodies used to treat cancer). Agarabi et al. J Bioreactor process parameter screening utilizing a Plackett-Burman design for a model monoclonal antibody. *J Pharamceut Sci* (manuscript in press).	FDA researchers are developing a systematic manufacturing approach to ensuring the quality of monoclonal antibodies, which are increasingly important as cancer therapeutics.
Detecting harmful adulterants. Drug adulteration or contamination with melamine is a potential public health concern as it is a known nephrotoxin. FDA researchers compared different analytical techniques (thermal analysis, X-ray diffraction, Fourier transform infrared (FT-IR), FT-Raman, and near-infrared spectroscopy) for their ability to detect a range of melamine levels in gelatin, a common component of drug capsules. They found that analyzed appropriately, near-infrared spectroscopy data yielded the most accurate model for quantifying melamine contamination. Cantor, Stuart L., Abhay Gupta, and Mansoor A. Khan. "Analytical Methods for the Evaluation of Melamine Contamination." *Journal of pharmaceutical sciences* 103.2 (2014): 539-544.	This research furnished valuable technical information to regulators and inspectors seeking to prevent melamine contamination in the pharmaceutical supply chain.
Ensuring the quality of protein therapeutics. Oxidation reactions can have important effects on the activity of biomolecules. FDA researchers used an immunologically based method to detect oxidation of large protein molecules in complex protein samples and human plasma stored with varying amounts of divalent iron, or at different temperatures and found this approach to be sensitive and specific. Uehara, H., & Rao, V. A. (2014). Metal-Mediated Protein Oxidation: Applications of a Modified ELISA-Based Carbonyl Detection Assay for Complex Proteins.	The study and its discussion of the many factors that can impact protein oxidation will assist in the development of manufacturing control strategies to mitigate this clinically relevant pathway for degradation of protein therapeutics.

Accomplishment	Significance
Pharmaceutical research, 1-11.	
Determining the safety parameters of a platelet safety device. Despite advances in bacterial detection and identification techniques, about 30 to 100 annual cases of sepsis are associated with transfusions of blood platelets to patients who need them. (Sepsis is a potentially life-threatening complication of an infection that occurs when chemicals released into the bloodstream to fight infection trigger inflammation throughout the body). However, treating platelets with UV light to kill contaminating bacteria and other microorganisms can cause changes in these cells that in some circumstances can trigger acute lung injury. FDA researchers developed a mouse model and used it to test the safety limits of a product that uses ultraviolet light and a photosensitizer (riboflavin) to treat platelets before transfusion. Chi, Xuan, Li Zhi, and Jaroslav G. Vostal. "Human platelets pathogen reduced with riboflavin and ultraviolet light do not cause acute lung injury in a two-event SCID mouse model." *Transfusion* 54.1 (2014): 74-85.	The study provided critical information for regulators about the safety limits of a widely used system for platelet decontamination that can help ensure the safety of transfused platelets. About two million units of platelets are given to patients each year.
Characterization of biological properties of multipotent stromal cells (MSCs) to improve product quality. Multipotent stromal cells (MSCs) are adult cells that have the ability to differentiate to become a variety of cell types (e.g., osteoblasts and fat cells). They are of significant clinical interest as potential cellular therapies to treat a variety of diseases because of their capacity for tissue repair and ability to modulate the immune system. Currently, there are hundreds of clinical trials to treat patients with a variety of diseases with these cells. Using automated fluorescence microscopy and other techniques, FDA researchers evaluated different populations of MSCs to quantify adipogenic potential (the ability to form fat cells), expansion capacity, and other characteristics of these cells. The capacity to form fat cells (adipocytes) varied among donor cell lines and decreased as cells were passaged. Lo Surdo, J. L., Millis, B. A., & Bauer, S. R. (2013). Automated microscopy as a quantitative method to measure differences in adipogenic differentiation in preparations of human mesenchymal stromal cells. *Cytotherapy,* 15(12), 1527-1540.	MSCs show great potential as a cellular therapy because of their ability to differentiate and suppress activation of the immune system. The quantitative approaches tested in this study can help investigators measure MSC quality and differences (between donors and according to cell passage) not revealed by conventional approaches, and may aid in the development of quality tests for products based on these cells.
Ensure FDA Readiness to Evaluate Innovative Emerging Technologies	
Understanding the interaction of nanomaterials with blood components. FDA researchers collaborated with the Nanotechnology Characterization Laboratory to develop a panel of *in vitro* assays for evaluating the effects of nanomaterials on blood platelets and endothelial cells, and in collaboration with researchers at NIST they elucidated the molecular mechanism of blood platelet activation by carbon nanotubes and the effect of carbon nanoparticles on endothelial cells. Assays developed using carbon and dendrimer nanoparticles are now being validated with other nanoparticles with the goal of working toward ASTM and ISO standards. Simak, J., •The Effects of Engineered Nanomaterials on Cultured Endothelial Cells in Dobrovolskaia and McNeil, eds, Handbook of Engineered Nanomaterials. (DOI: 10.1142/9789814390262_0008)	FDA researchers are developing assays that will be needed to ensure the safety of nano-sized biologics as drug delivery systems or as components of imaging methodologies.

Accomplishment	Significance
Interpreting next-generation sequencing data. A critical step in analyzing NGS sequencing data is alignment of short sequence reads to obtain the full sequence. FDA researchers have introduced a new algorithm (HIVE-hexagon DNA sequence aligner) that reduces the memory footprint required for alignment of NGS data and, therefore, the overall time needed for the alignment. Santana-Quintero, L., Dingerdissen, H., Thierry-Mieg, J., Mazumder, R., & Simonyan, V. (2014). HIVE-hexagon: high-performance, parallelized sequence alignment for next-generation sequencing data analysis. *PloS one*, 9(6), e99033.	NGS technology produces sets of data that are so large and complex that they overwhelm the ability of most computer systems to store, search, and analyze them, or transfer the information to other computer systems. The new algorithm will make it more feasible to incorporate data from next-generation sequencers into drug development (e.g. of personalized medicines) and regulatory review.
Using next-generation sequencing data to understand resistance to antiviral treatment. Using next-generation sequencing data submitted to the Agency, FDA researchers analyzed the association of specific genetic changes (mutations) in the virus that causes hepatitis C with resistance to a treatment and mapped them to protein structures. Donaldson, E. F., Harrington, P. R., O'Rear, J. J., & Naeger, L. K. (2014). Clinical evidence and bioinformatics characterization of potential hepatitis C virus resistance pathways for sofosbuvir. Hepatology, published ahead of print (doi 10.1002/hep2735.	In addition to the specific results on the mechanism of viral resistance in treated patients, this study was a significant advance towards developing a set of analytic procedures for evaluation of the next-generation sequencing data that is expected to accompanying many drug applications.
Harness Diverse Data Through Information Sciences to Improve Health Outcomes	
Predicting drug-drug interactions. FDA has developed a publicly available drug transporter database that includes information on membrane transport proteins that are critical to predicting drug exposures in patients. The database collects information on expression levels, subcellular localization, known substrates, transport kinetics, and known drug-drug interactions attributable to the transporter. The database is intended as a free public resource to diverse stakeholders seeking to develop safer medications. Morrissey, K. M., Wen, C. C., Johns, S. J., Zhang, L., Huang, S. M., & Giacomini, K. M. (2012). The UCSF-FDA TransPortal: a public drug transporter database. *Clinical Pharmacology & Therapeutics,* 92(5), 545-546.	A publically available database developed by FDA will help drug developers determine what experiments or analyses should be conducted to check for transporter-mediated drug interactions and identify promising transporter candidates for the testing of possible genetic influences.
Determining safe and effective doses for unstudied populations. Using modeling and simulation approaches, FDA scientists have developed models to bridge existing clinical data to guide dosing recommendations in unstudied populations. For example a physiologically based pharmacokinetic model incorporating information on acetaminophen's (Tylenol's) physicochemical properties and its elimination pathways, as well as extensive anatomic and physiologic data, was developed to guide dosing recommendations in children, and similar modeling approaches have been instrumental in developing labeling recommendations for the antibiotic Piperacillin, the anticoagulant Dabigatran (used to treat COPD), and the antipsychotic Paliperidone. Jiang et al., (2013) Application of physiologically based pharmacokinetic modeling to predict acetaminophen metabolism and pharmacokinetics in children. Pharmacometrics and Systems Pharmacology, 2 e80.	FDA researchers have constructed pharmacokinetic models that incorporate diverse data and can be used to make informed decisions concerning the treatment or further investigation of populations for which data from randomized clinical trials is lacking.

Accomplishment	Significance
Assessing post marketing drug safety by active surveillance. Angiotensin-converting enzyme inhibitors (ACEIs), which target the renin-angiotensin-aldosterone system, are widely used in patients with hypertension or ischemic heart disease. FDA researchers found that compared with beta-blockers, ACEIs were associated with an approximately three-fold higher risk for angioedema. Toh et al., Archives of Internal Medicine, 12:1582-1589.	This is one of over 30 surveillance projects that were undertaken to test the pilot system.
Facilitate Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security	
An alternative and rapid way to produce a vaccine against a potential pandemic influenza virus. FDA researchers demonstrated that bacterially expressed recombinant HA1 immunogens may provide an alternative H5N1 vaccine platform. When combined with the appropriate adjuvant, they are likely to generate high-affinity antibodies with the capacity to neutralize heterologous strains, control virus replication in the upper respiratory tract, and reduce virus transmission. Plant E.P., Ye Z. (2014). Chimeric NA and mutant PB1 gene constellation improves growth and yield of H5N1 vaccine candidate virus. *J Gen Virol* 2014 [Epub ahead of print].	The work could provide an alternative to current methods for vaccine production, thus saving several months of manufacturing time. In addition, this was the first study to show the role of antibody avidity for the HA1 globular head domain in reducing viral loads in the upper respiratory tract.
Evidence supporting continued use of a vaccine against a pandemic influenza virus. FDA researchers did a meta-analysis to look for a potential link between Guillain-Barré syndrome (GBS) and the use of the influenza A (H1N1) pandemic vaccine. The study concluded there were 1.6 excess cases of GBS per million people vaccinated, a modest risk consistent with previous estimates of GBS after seasonal influenza vaccination. Salmon, D. A., Proschan, M., Forshee, R., Gargiullo, P., Bleser, W., Burwen, D. R., & Lurie, N. (2013). Association between Guillain-Barré syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: a meta-analysis. *The Lancet*, 381(9876), 1461-1468.	The data support the conclusion that the benefits of the 2009 H1N1 vaccines outweighed the risks, which is an important reassurance for clinicians and consumers given the morbidity and mortality caused by the 2009 H1N1 influenza pandemic.
Understanding a route of anthrax infection. FDA scientists developed a murine model for intestinal anthrax infection and characterized effect of infection on the immune system and the gastrointestinal tract and response of the infected animals to antibiotic therapy. Xie, T., Sun, C., Uslu, K., Auth, R. D., Fang, H., Ouyang, W., & Frucht, D. M. (2013). A new murine model for gastrointestinal anthrax infection. *PloS one*, 8(6), e66943.	The model may prove useful in the evaluation for regulatory purposes of therapies that target anthrax lethal toxin or edema toxin.
Quantitating levels of a critical antiviral drug. FDA researchers developed a	This work will be useful in the

Accomplishment	Significance
highly sensitive assay to quantitate the level of the influenza antiviral Tamiflu (oseltamivir) and its active metabolite (oseltamivir carboxylate) in blood samples. Ilyushina NA, Donnelly RP, In vitro anti-influenza A activity of interferon (IFN)-lambda1 combined with IFN-beta or oseltamivir carboxylate. *Antiviral Research* 2014 Nov; 111:112-20.	development of appropriate dosing for at-risk populations such as pregnant women.
Towards an improved vaccine for anthrax. FDA scientists are using protein engineering and nanoparticle formulations to improve vaccination against anthrax based on the anthrax protective antigen. Manish, M., Rahi, A., Kaur, M., Bhatnagar, R., & Singh, S. (2013). A single-dose PLGA encapsulated protective antigen domain 4 nanoformulation protects mice against Bacillus anthracis spore challenge. *PloS one*, 8(4), e61885.	Protein engineering and encapsulation of the anthrax antigen may allow investigators to develop a safer and more effective vaccine for this major bioterrorism agent.
Faster development of flu vaccines. Researchers at FDA demonstrated an alternative and rapid way to produce a vaccine against a potential pandemic influenza virus. These investigators showed that bacterially expressed recombinant HA1 immunogens, which contain a high percentage of functional oligomers, may provide an alternative H5N1 vaccine platform. When combined with the appropriate adjuvant, they are likely to generate high-affinity antibodies with the capacity to neutralize heterologous strains, control virus replication in the upper respiratory tract, and reduce virus transmission. Verma, S., Dimitrova, M., Munjal, A., Fontana, J., Crevar, C. J., Carter, D. M., ... & Golding, H. (2012). Oligomeric recombinant H5 HA1 vaccine produced in bacteria protects ferrets from homologous and heterologous wild-type H5N1 influenza challenge and controls viral loads better than subunit H5N1 vaccine by eliciting high-affinity antibodies. *Journal of virology*, 86(22), 12283-12293.	Safe and effective recombinant HA-based anti-H5N1 vaccines could provide an alternative to in vitro (chicken eggs) or in vivo (reverse genetics) techniques, thus saving several months of manufacturing time, since the HA gene of the newly circulating strain is available shortly after virus isolation.
Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions About Regulated Products	
Characteristics of effective direct-to-consumer advertising. FDA conducted a study to determine if comparative claims in direct-to-consumer (DTC) ads influence perceptions and recall of drug information. Variables studied in the advertisements included whether a comparative efficacy claim was made, whether the competitor product was named or unnamed, the type of comparison, and whether the ad was print or video. O'Donoghue, A.C., Williams, P.A., Sullivan, H.W., Boudewyns, V., Squire, C., & Willoughby, J.F. (2014). Effects of comparative claims in prescription drug direct-to-consumer advertising on consumer perceptions and recall. Social Science and Medicine, 120, 1-11.	Overall, the results suggest that comparative claims in DTC ads could mislead consumers about a drug's efficacy and risk; therefore, caution should be used when presenting comparative claims in DTC ads.
Communicating efficacy information in direct-to-consumer advertising. FDA conducted two studies to examine the impact of adding quantitative information about product benefits to DTC ads. The first study examined whether adding placebo rate information and changing the framing of the information to include only the number who benefit (positive frame) versus the number who benefit and the number who do not benefit from the drug (mixed frame) helps consumers understand the risk information. O'Donoghue, A. C., Sullivan, H. W., & Aikin, K. J. (2014). Randomized study of	Results showed that adding placebo rates to DTC ads may be useful for consumers, whereas the evidence does not support the use of mixed frames.

Accomplishment	Significance
placebo and framing information in direct-to-consumer print advertisements for prescription drugs. Annals of Behavioral Medicine, 1-12. The second study investigated the level of product efficacy (high or low), the statistical format of that information (frequency, percent, frequency plus percent, relative frequency, or frequency plus relative frequency), and ways in which that information can be expressed visually (pie chart, bar chart, table, or pictograph). O'Donoghue, A.C., Sullivan, H.W., Aikin, K.J., Chowdhury, D., Moultrie, R.R., & Rupert, D.J. (2014). Presenting efficacy information in direct-to-consumer prescription drug advertisements. Patient Education and Counseling, 95(2), 271-280. doi: 10.1016/j.pec.2013.12.010. Available at http://www.sciencedirect.com/science/article/pii/S0738399113005247	In general, providing quantitative benefit information in DTC ads increased participants' ability to accurately report the benefits of the drug in quantitative terms. Further, adding visual aids, in particular bar charts and tables, increased participants' ability to accurately report the drug's benefits.
Perception of prescribing information in drug labels. FDA conducted an online survey of primary care physicians' use of the newly formatted drug prescribing information (PI) in drug labels and how it influenced their perceptions in terms of perceived risk, perceived benefit, and intention to prescribe. Sullivan, H. W., O'Donoghue, A. C., & Aikin, K. J. (2014). Primary care physicians' use of FDA-approved prescription drug labels. *The Journal of the American Board of Family Medicine*, 27(5), 694-698.	The results suggested that the information in the prescribing information section of the label could affect physician decision making, but it did not support further reorganization of the PI section.
Understanding medicine abuse. FDA conducted a survey, in the form of interviews with physicians on factors related to prescription abusable medications, including opioids, as the first step in building a multi-media peer-to-peer provider education campaign on tackling the prescription abuse epidemic.	This study will inform a multi-media peer-to-peer provider education campaign designed to prevent abuse of opioids and other medications.

2. Collaborative Research

In addition to the intramural research activities described above, FDA continued to broaden its engagement with the external scientific community using a variety of mechanisms. These collaborative initiatives performed critical research in such areas as data standardization, biomarker development, clinical studies of cardiotoxicity, and the use of gene expression data for purposes of drug development. Note that FDA is engaged with over 20 public-private partnerships, many of which are relevant to PDUFA goals. A more complete list can be found in Section V.

Examples of Public-Private Partnerships to Further Drug Development[13]

Public-Private Partnership	Participants	Mission	Recent (FY 2013-2014) Accomplishments
The Coalition Against Major Disease (CAMD) Consortium	Scientists from pharmaceutical and biotechnology companies, patient advocacy organizations, academic advisors and representatives from regulatory agencies	Develop new tools (biomarkers and disease progression models) and methods that can be applied during the development of new treatments for neurodegenerative diseases.	Developed quantitative simulation tool that models the progression of Alzheimer's Disease that was endorsed by FDA and the European Medicines Agency and will help investigators make informed decisions about design of clinical trials of treatment for this disease.
Cardiac Safety Research Consortium (CSRC)	Stakeholders from industry, academia, and government	Advance scientific knowledge on cardiac safety for new and existing medical products by building a collaborative environment based upon the principles of the FDA's Critical Path Initiative as well as other public health priorities.	Initiated clinical study in healthy subjects to determine if the dedicated thorough QT study can be replaced by analysis of electrocardiogram data generated from First-in-Man single ascending dose studies. Published numerous reports on cardiovascular safety in the context of drug development. Numerous think tanks and workshops (a complete list is publically available).[14]
MicroArray Quality Control-III (MAQC-III)	Major providers of microarray platforms and RNA samples, National Institutes of Health (NIH), Environmental Protection Agency (EPA), National Institute of Standards and Technology (NIST), academic laboratories, and other stakeholders.	Assess the technical performance of next-generation sequencing platforms by generating benchmark datasets with reference samples and evaluating advantages and limitations of various bioinformatics strategies in RNA and DNA analyses.	Comprehensively assessed RNA sequencing performance for junction discovery and differential expression profiling and compared it to microarray and quantitative PCR (qPCR) data using complementary metrics. Provided cumulative SEQC data sets with >100 billion reads (10 Tb) as a public resource for testing future developments of RNA-seq, as required in clinical and regulatory settings.

[13] A comprehensive table of such partnerships is provided in Part V of this report.
[14] www.cardiac-safety.org/think-tanks

ii. Adopting Advances in Regulatory Science to Promote the Goals of PDUFA

FDASIA explicitly required FDA to –

> Set forth how the Food and Drug Administration will ensure that advances in regulatory science for medical products are adopted, as appropriate, on an ongoing basis and in a manner integrated across centers, divisions, and branches of the Food and Drug Administration, including by senior managers and reviewers, including through the
>
> (A) development, updating, and consistent application of guidance documents that support medical product decision-making; and
>
> (B) adoption of the tools, methods, and processes under section 566 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360 bbb–5).

Adoption of regulatory science occurs through a variety of mechanisms: Through public workshops, the Agency receives and evaluates new scientific information and considers its regulatory implications. By convening advisory committees, FDA solicits advice from external experts—sometimes on the science evidence that would support a specific regulatory decision, e.g., a drug approval, but often on far-reaching questions posed by emerging sciences. To stay abreast of scientific developments, reviewers and staff organize and attend focused scientific training. As the level of scientific certainty surrounding a particular issue rises to a level that warrants application in a regulatory setting, FDA issues guidance to industry or official communications to prescribers and patients. Specialized processes, involving iterative interactions with sponsors, such as the Drug Development Tools programs, are designed improve the integration of scientific advances into regulatory decision making on biomarkers, disease models, and clinical assessment tools. The following are a few examples of how FDA has adopted and incorporated scientific advances to further the intent of PDUFA (see Section V for a compilation of these activities, many of which apply to more than one user fee agreement).

1. Training to help realize the intent of PDUFA

Examples of Recent Courses Relevant to Drug Development

Course Title	Times Offered (No. of lectures if > 1)
Current Good Manufacturing Practices (cGMP)	3
Introduction to Design and Conduct of Clinical Trials	2
Global Drug Development and its Impact on CDER's Review Process	1
Advanced Topics in Pharmacoepidemiology	1
Introduction to Pharmacoeconomics,	1
2014 MCMi Regulatory Science Symposium	1
CDER Seminars (32 lectures on diverse topics)	1 (32)

Course Title	Times Offered (No. of lectures if > 1)
Clinical Genomics, Scientific and Regulatory Aspects	1
Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics	1
Global Drug Development and its Impact on CDER's Drug Review Process Symposium	1
Infectious Disease Journal Club	1(67)
Investigational New Drug Regulations and Policies	5
Medical Countermeasures Lecture Series	1(6)
Medical Officer Rounds: Gastroenterology and Inborn Errors Products	1 (18)
Medication Errors	1
New NIH Drug Information Databases Useful to FDA Reviewers	1
2013 and 2014 OND Rare Diseases Program Training Unmet Medical Need: Thinking Outside the Regulatory Box	2
Recent Advances in Targeted Delivery of Biologics and Small Molecule Drugs Symposium	2
Toxicology for Non-Toxicologists	1
Chemistry for Non-Chemists	2

2. Workshops and advisory committee meetings to foster drug development and ensure safety and efficacy

Examples of Recent Workshops and Advisory Committee Meetings on Topics in Regulatory Science That Helped Realize the Intent of PDUFA

Workshop or Meeting	Date	Purpose	FDA Priority Area[15]
FDA/PQRI Conference on Evolving Product Quality	September 16-17, 2014	Provide a forum for industry, academia, regulatory and other pharmaceutical professionals to discuss ideas and resources related to pharmaceutical quality.	3
Synergizing Efforts in Standards Development for Cellular Therapies and Regenerative Medicine Products	September 13, 2014	Bring together a broad range of stakeholders to discuss current and future standards development activities involving cellular therapies and regenerative medicine products.	4
Cardiovascular Outcomes Safety Trials; Part 15 Hearing	August 11, 2014	Initiate constructive discussion among regulators, researchers, health care providers, representatives from the pharmaceutical industry and health care organizations, and the general public, about appropriate handling of interim analysis results of ongoing cardiovascular outcome trials (CVOTs).	2
The Development of New Antibacterial Products: Charting a Course for the Future	July 30-31, 2014	Explore key issues and challenges related to antibacterial product development and discuss the development of streamlined regulatory pathways for bringing new antibacterial drugs to market.	2
Next-Generation Sequencing Technology, Data Formats Standardization and Promotion of Interoperability Protocols	May 19, 2014	Initiate discussions with stakeholders about data format standards required to facilitate development of innovative medical products that rely on “Next Generation Sequencing” technology.	2
Pioneering Statistical Approaches to Accelerate Drug Development through Adaptive Trial Designs	March 27, 2014	Explore statistical and operational issues related to the use of adaptive clinical trials in the curative disease setting, with particular focus on trial designs that allow for consideration of accelerated approval based on interim analysis with respect to intermediate endpoints (with the final analyses based on a clinical benefit endpoint).	2

[15] Priorities related to medical products and devices 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, 7) Facilitate Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security, and 8) Strengthen Social and Behavioral Science to Help Consumers and Professionals Make Informed Decisions about Regulated Products.

Workshop or Meeting	Date	Purpose	FDA Priority Area[15]
Application of Physiologically –Based Pharmacokinetic Modeling to Support Dose Selection	March 15, 2014.	Explore the use of PBPK models for assessing the effect of various intrinsic and extrinsic factors in order to inform dose optimization.	2
Nanomaterial Drug Products: Current Experience and Management of Potential Risks	January 14-15, 2014	Review analytical science and methods for characterizing nanomaterials; Discuss their application to the characterization and quality control of drug products; Discuss approaches to the management of potential risks of nanomaterials in drug products starting from early drug development and throughout product lifecycle; get perspectives from international regulatory agencies and standards setting organizations on the use of nanotechnology in pharmaceutical products; and discuss areas where additional research may be needed.	4
Meta-Analyses of Randomized Controlled Clinical Trials for the Evaluation of Risk to Support Regulatory Decisions	November 15, 2013	Initiate discussion and information sharing among regulators, researchers, representatives from the pharmaceutical industry and others on the conduct, assessment, interpretation and development of best practices of meta-analyses of randomized controlled clinical trials to evaluate safety risks associated with the use of human drugs or biological products within the framework of regulatory decision making.	2
Impact of Approved Drug Labeling on Chronic Opioid Therapy	February 7-8, 2013	Obtain information, particularly scientific evidence, such as study data or peer-reviewed analyses, on issues pertaining to the use of opioid drugs in the treatment of chronic pain. These issues include: diagnosis and understanding of patient pain, understanding and adhering to the labels of pain-treating products, limiting opioid prescriptions and use, and abuse and misuse of opioid medicines.	8
Advisory Committee Meetings			
Reproductive Health Drugs- Drug Safety Risk Management	September 17, 2014	Consider and evaluate the efficacy and safety of testosterone undecanoate delivered via intramuscular injection as replacement therapy in adult males for conditions associated with a deficiency or absence of testosterone.	2
Cellular, Tissue and Gene Therapies Advisory Committee	October 22-23, 2013	Discuss oocyte modification in assisted reproduction for the prevention of mitochondrial disease or treatment of infertility	4
Pharmaceutical Science and Clinical Pharmacology.	September 15, 2013	Discuss optimal strategies for the evaluation, interpretation, and communication of drug-drug interaction (DDI) information, including (1) best practices in DDI communication through prescription drug product labels; (2) appropriate criteria for determining whether or not to describe DDI information derived from the literature in product labels; and (3) how package insert information on DDIs is used by various end-users in decision making and/or communication.	8

3. Guidance development

Noteworthy Guidances Relevant to PDUFA and Addressing Different Priority Areas

Title and Description	Date
Facilitate Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security	
Highly Multiplexed Microbiological/Medical Countermeasure in Vitro Nucleic Acid Based Diagnostic Devices This guidance provides industry and FDA staff with recommendations for studies to establish the analytical and clinical performance of highly multiplexed microbiological/medical countermeasure in vitro nucleic acid based diagnostic devices (HMMDs) for detecting and identifying multiple pathogen nucleic acids from single human specimen or culture.	August 2014
Harness Diverse Data through Information Sciences to Improve Health Outcomes	
Providing Regulatory Submissions in Electronic Format —Standardized Study Data This guidance specifies how to submit standardized study data in regulatory applications supporting new drugs and biologics.	February 2014
Ensure FDA Readiness to Evaluate Innovative Emerging Technologies	
Qualification Process for Drug Development Tools This document describes the process for qualifying biomarkers, animal models, and clinical outcome assessment tools under the Agency's Drug Development Tools (DDT) programs. It provides a framework for interactions between FDA and the entity developing the tool, describes the kinds of data that should be submitted to support tool qualification, and creates a mechanism for formal review of the data to ultimately qualify the DDT.	January 2014
Support New Approaches to Improve Product Manufacturing and Quality	
International Conference on Harmonisation; Draft Guidance on Elemental Impurities This guidance is intended to develop a harmonized approach for the control of elemental impurities to help industry avoid the uncertainty and duplication of work resulting from differing requirements worldwide. It is expected to provide appropriate safety-based limits for the control of elemental impurities, consistent expectations for test requirements and regulatory filings, and a global policy for limiting elemental impurities, both qualitatively and quantitatively, in drug products and ingredients.	October 2013
Modernize Toxicology to Enhance Product Safety	
Endocrine Disruption Potential of Drugs: Nonclinical Evaluation This guidance provides recommendations to sponsors of investigational drugs regarding nonclinical studies intended to identify the potential for a drug to disrupt the endocrine system. It describes how endocrine disruption potential is assessed using a standard battery of nonclinical tests; explains potential outcomes of such testing and the consequences of such outcomes; and identifies situations in which additional clinical and nonclinical studies should be considered to more fully characterize the endocrine disruption potential of a drug.	September 2013
Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes	
Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products This guidance describes a wide range of strategies drug developers may use to prospectively select a population in which a drug effect is more likely to be detected compared with an unselected population. For each strategy the guidance outlines the disadvantages and advantages and addresses important issues of interpretation.	December 2012

4. The Drug Development Tools Programs

The Drug Development Tool (DDT) Qualification programs were created by FDA to provide a framework for development and regulatory acceptance of scientific tools, including biomarkers, clinical outcome assessments, and animal models, for use in drug and biologic development programs. The programs evaluate the evidence that a DDT can be reliably used and the results interpreted within a given context of use, then that new science is integrated into tools that accelerate drug development through qualification.[16]

Status of Projects in the Drug Development Tools ProgramCurrent Stage of DDT	All DDTs	Animal Models	Biomarkers	Clinical Outcome Assessments
Active Projects	79	7	24	48
Initiation Stage	22	4	0	17
Number in Consultation and Advice Stage	52	3	21	29
Review Stage	5	0	3	2
Qualified	4	0	3	1

5. Critical Path to Innovation Meeting (CPIM) Program

The CPIM Program was inaugurated in 2013 to create a forum in which the FDA and investigators from industry, academia, patient advocacy groups, and government could communicate to improve efficiency and success in drug development. The goals of the CPIM are to discuss a methodology or technology proposed by the meeting requester and for FDA to provide advice on how this methodology or technology might enhance drug development. The meetings allow FDA to become more familiar with prospective innovations in drug development, broadening its regulatory perspective. The discussions and background information submitted through the CPIM are confidential, drug product-independent, and nonbinding on both FDA and CPIM requesters.

In 2015, FDA issued a guidance describing the purpose, scope, documentation, and administrative procedures for a CPIM and delineating appropriate topics for such meetings.[17]

[16] Additional information is available at www.fda.gov/drugs/developmentapprovalprocess/drugdevelopmenttoolsqualificationprogram/default.htm.
[17] Due to their confidentiality, we are not listing recent CPIM meetings here. The CPIM guidance is available at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM417627.pdf.

II. Regulatory Science to Ensure Access to Safe and Effective Generic Drugs under the Generic Drug User Fee Agreement

GDUFA authorized user fees from the generic drug industry to supplement FDA's costs of reviewing generic drug applications and inspecting facilities. User fees may also support FDA research that underpins the Agency's guidance for developing new generic products and that improves FDA's review process for generic drug applications. The ultimate goal is ensuring that patients have access to safe and effective generic drugs.

In 2013, based on internal CDER discussions, public meetings, and comments submitted to the Agency, FDA developed the following five regulatory research priorities for FY 2014:[18]

1. Post-market Evaluation of Generic Drugs
2. Equivalence of Complex Products
3. Equivalence of Locally-Acting Products
4. Therapeutic Equivalence Evaluation and Standards
5. Computational and Analytical Tools

Since enactment of GDUFA, FDA's Office of Generic Drugs (OGD) has supported internal research by purchasing equipment for FDA labs, supporting FDA research fellows, and initiating external research through contracts and grant awards.

The research projects FDA committed to in FY 2013 are still ongoing and it is too early to review their accomplishments. This section describes these projects and indicates the GDUFA and FDA regulatory science priorities to which they apply. Also included are examples of recent (FY 2013–FY 2014) accomplishments in regulatory science from projects funded prior to GDUFA that are relevant to the intent of this user fee agreement. Select guidances in which FDA recommends scientific advances that will help industry develop safe and effective generics are described.

[18] A full description of these priorities is available at www.fda.gov/Drugs/NewsEvents/ucm367997.htm.

i. Addressing Scientific Gaps to Further the Development of Safe and Effective Generic Drugs

1. Current research supporting development of safe and effective generics

Ongoing Research Supporting Generic Drug Development Organized According to Priority Areas

Fiscal Year	Project Title and Grantee(s)	Project Description	GDUFA Priority[19]	FDA Priority[15]
2014	Characterization of Epilepsy Patients at Risk for Adverse Outcomes Related to Switching Antiepileptic Drug Products University of Maryland	The objective of this contract is to evaluate the potential factors that may cause generic brittleness (GB) in epilepsy patients (i.e. those sensitive to antiepileptic drug formulation changes). The outcome of this exploratory research will uncover potential factors causing patients to be GB and assess whether those factors result in pharmacokinetic (PK) differences between brand and generic drugs in GB individuals.	4	1, 2
2014	Bioequivalence and Characterization of Generic Drugs Vince & Associates Clinical Research, Inc.	As part of continuous monitoring of approved generics, this contract will support bioequivalence studies of approved generic products including bioequivalence (BE) between: generic and brand methylphenidate hydrochloride extended release tablets, and (2) BE between a reference listed drug (RLD) and generic warfarin sodium product stored under different conditions. The outcome of the research will provide evaluation of the use of replicate design BE studies for generic methylphenidate hydrochloride ER products and inform the development of clinically relevant quality standards for warfarin sodium products.	1	2

[19] GDUFA Priorities are 1) Post-market Evaluation of Generic Drugs, 2) Equivalence of Complex Products, 3) Equivalence of Locally-Acting Products, 4) Therapeutic Equivalence Evaluation and Standards, and 5) Computational and Analytical Tools.

Fiscal Year	Project Title and Grantee(s)	Project Description	GDUFA Priority[19]	FDA Priority[15]
2014	Pharmacometric Modeling and Simulation for Generic Drugs Evaluation University of Maryland Baltimore (2), University of Florida, and University of Utah	The goal of these grants is to develop quantitative pharmacometric models for generic drug evaluation in the following areas: (1) narrow therapeutic index drugs, (2) generic drug substitutability and post-marketing risk assessment, and (3) partial area under the curve as bioequivalence criteria. The outcome of the project will aid in the development of the following: (1) models and modeling approaches that will help FDA classify drugs as having a narrow therapeutic index and identify those products that have a clinical use profile that requires tighter control of product quality and equivalence attributes, (2) pharmacometric approaches (including clinical trial simulation and clinical use/substitution simulation) that will aid OGD in the evaluation of post-market risk and the interpretation of post-market adverse event reports or product substitution complaints, and (3) modeling and simulation tools that will aid FDA in identifying which generic drug products require greater degrees of pharmacokinetic profile similarity in order to assure therapeutic equivalence.	2, 4, 5	2, 5

Fiscal Year	Project Title and Grantee(s)	Project Description	GDUFA Priority[19]	FDA Priority[15]
2014	Physiologically based absorption and pharmacokinetic modeling and simulation for non-gastrointestinally absorbed drug products in humans University of South Australia , Simcyp, Ltd., Simulations Plus, Inc, CFD Research Corporation (2), State University of New York at Buffalo, Applied Research Associates Inc.	The goal of this grant is to develop physiologically-based absorption and pharmacokinetic (PK) models for complex drug products, such as locally-acting drug products and non-biological complex parenteral drug products. Research should impact generic drug product guidance preparation, aid the development of generic formulations by industry, and evaluate generic drug products for physiologically-based pharmacokinetic modeling and simulation of: (1) dermal absorption, (2) ocular absorption, (3) complex parenteral drug products (including liposomes, nanosuspension, micelles, microspheres, implants, and hydrogels), (4) lung absorption via oral inhalation, and (5) absorption from nasally delivered products (including nasal solutions, solutions and suspensions as well as nasal insufflation as a potential route of abuse). The outcome of these projects will aid in understanding the complex interplay between product attributes and human physiology and will help develop new bioequivalence approaches for locally-acting drugs and complex parenteral drug products.	2, 3, 4, 5	2, 5
2014	Development of Clinically Relevant In Vitro Performance Test for Generic Orally-Inhaled Drug Products (OIDPs) Virginia Commonwealth University	The goal of this project is to investigate if realistic physical mouth-throat models provide better predictability than pharmaceutical induction port assembly for aerodynamic particle size distribution (APSD) characterization of OIDPs. This research will provide a more realistic APSD characterization method that can be used as a pharmaceutical development tool in the early stages of OIDP development.	2, 3	3

Fiscal Year	Project Title and Grantee(s)	Project Description	GDUFA Priority[19]	FDA Priority[15]
2014	Dissolution Methods for Suspension and Emulsion Ocular Drug Products University of Eastern Finland, Texas A&M University	The goal of these studies is to investigate dissolution methods for an ocular suspension or emulsion and to analyze their capabilities to detect manufacturing differences, predict in vivo performance, and evaluate method robustness. Study outcomes will help FDA develop recommendations that determine bioequivalence of generic ocular suspension and emulsion drug products.	2	3
2014	Dissolution Methods for Semisolid Ocular Drug Products University of Connecticut	The goal is to investigate dissolution methods for a parenteral sustained release dosage form and to analyze their capabilities to detect manufacturing differences, predict in vivo performance, and evaluate method robustness. The outcome from this study will help the FDA in developing recommendations to determine bioequivalence of generic ocular semisolid drug products.	2, 4	3
2014	Dissolution Methods for Microsphere and Implant Drug Products University of Connecticut, Akina, Inc., and University of California San Diego	The goal is to investigate dissolution methods for a parenteral sustained release dosage form and to analyze their capabilities to detect manufacturing differences, predict in vivo performance, and evaluate method robustness. The outcome will help the FDA in developing recommendations to determine bioequivalence of generic parenteral sustained release drug products.	2, 4, 5	3

Fiscal Year	Project Title and Grantee(s)	Project Description	GDUFA Priority[19]	FDA Priority[15]
2014	Characterization of Critical Quality Attributes for Semisolid Topical Drug Products University of Mississippi and University of South Australia	The goal of these studies is to characterize key physical and chemical qualities of different semisolid topical drug products (e.g., creams, ointments, gels), identify methods to measure these quality attributes, characterize formulation and manufacturing parameters that alter the arrangement of matter in these drug products, and utilize in vitro and/or in vivo measures of product performance to correlate variations in critical quality attributes with a failure mode for a drug product. The intended outcome is to understand how specific aspects of drug product manufacturing and quality influence product performance in vitro, and how this correlates with clinical performance in vivo.	2, 3, 4	3, 4
2014	Evaluation of Plasma NTBI levels in Hemodialysis Patients Treated with Generic and Reference Sodium Ferric Gluconate University of Maryland, Baltimore	The goal of this study is to conduct in vivo studies to compare plasma total iron (TI), transferrin bound iron (TBI), non-transferrin bound iron (NTBI), and oxidative stress levels after intravenous administration of RLD and generic sodium ferric gluconate injections in healthy subjects. The purpose is to confirm the in vivo equivalence of generic iron complex products.	4	2
2014	Effect of Therapeutic Class on Generic Drug Substitutions Johns Hopkins University	The goal of this study is to rank order generic drugs based on therapeutic class with low generic substitution/acceptance rate and analyze factors affecting the generic substitution in each therapeutic class. Study results will ascertain the extent to which bias against generic drugs affects generic substitution.	4	8

Fiscal Year	Project Title and Grantee(s)	Project Description	GDUFA Priority[19]	FDA Priority[15]
2014	Post-Market Surveillance Evaluation of Authorized Generic Drug Products Brigham and Women's Hospital and Auburn University	The project goal is to compare authorized generics (products nearly identical to the brand product, but marketed under a different label) to brand name and other generic drugs to evaluate existing tools and to develop new methods to monitor the safety, efficacy, usage, and substitution patterns of generic drugs in different therapeutic categories. Study results will ascertain the extent to which bias against generic drugs affects generic substitution.	1	5, 8
2014	Pharmacokinetic/Pharmacodynamic (PK/PD) Studies of Generic Cardiovascular Drugs in Hypertensive Patients University of Florida	The goal of this project is to conduct a prospective PK/PD study to identify the key product attributes and patient factors that may impact the PK/PD and therapeutic equivalence of metoprolol products. The outcome from the PK/PD study will help establish scientific and regulatory standards for assuring therapeutic equivalence of generic metoprolol products.	4	2
2014	Pharmacokinetic/Pharmacodynamic (PK/PD) Studies of Methylphenidate Extended Release Products in Attention Deficit Hyperactivity Disorder (ADHD) Patients Massachusetts General Hospital	The purpose of this project is to conduct a PK/PD study in pediatric attention deficit hyperactivity disorder patients (6-12 years of age) to link the PK profiles to the time-course of PD activity of methylphenidate ER products. The link may identify additional PK metrics that impact the therapeutic equivalence of these products. A study simultaneously collecting individual PK and PD data in pediatrics has not yet been performed for methylphenidate ER products, and these data can improve existing PK/PD models for these products. The PK/PD study will help to establish scientific and regulatory standards for assuring therapeutic equivalence of generic methylphenidate extended release products.	2, 4	2

Fiscal Year	Project Title and Grantee(s)	Project Description	GDUFA Priority[19]	FDA Priority[15]
2014	Effect of Different Preparation Methods on the In vitro and In vivo Performance of Solid Dispersion Formulations Purdue University, West Lafayette	The goal of this study is to investigate the in vitro and in vivo performance of solid dispersion drug products made from different manufacturing processes or polymer carriers, as well as their performance consistency during storage and among batches. The outcome will help to identify critical process parameters and critical quality attributes for solid dispersion made from different preparation methods and develop discriminating analytical methods.	2, 5	3
2014	Prospective Studies on the Impact of Generic Immunosuppressants on Acute Rejection and Long Term Graft survivals University of California, Los Angeles	The goal of this study is to conduct prospective clinical studies to investigate the impact of generic immunosuppressants on short term acute rejection and long term patient graft survival. The outcome of this study will help respond to public concerns regarding the interchangeability of generic immunosuppressants and improve review practices of generic immunosuppressants, if necessary. The study outcome will be compared to retrospective analyses to provide comprehensive perspectives and better research options regarding generic immunosuppressant interchangeability.	4	2
2014	Retrospective Analysis on the Impact of Generic Immunosuppressant on Acute Rejection and Long Term Graft Survivals Arbor Research Collaborative for Health	The goal of this study is to conduct a retrospective analysis of the impact of generic immunosuppressants on short term acute rejection and long term patient and graft survival since the introduction of generic immunosuppressants. The outcome of this study will respond to public concerns regarding the interchangeability of generic immunosuppressants and improve review practices for generic immunosuppressants.	4	2

Fiscal Year	Project Title and Grantee(s)	Project Description	GDUFA Priority[19]	FDA Priority[15]
2014	Evaluation of Dissolution Methods for Liposomal Drug Products ZoneOne Pharma, Inc.	This study aims to evaluate different in vitro release assays in terms of their capacities to detect formulation differences and predict in vivo release of liposomal drug products. The study outcome will advance the regulatory review process and ultimately improve public access to quality generic liposomal drug products detecting formulation differences and predicting in vivo release.	5	3
2014	Development of an Integrated Mathematical Model for Comparative Characterization of Complex Molecules Massachusetts Institute of Technology	The study goal is to construct a robust set of integrated algorithms or 'tools' to determine the extent of characterization required for establishing equivalence of complex mixtures. The outcome from this study will be improved tools to compare equivalence of complex mixtures.	2, 5	1, 5
2014	**Development of Process Simulation and Modeling Tools for Integrated Pharmaceutical Manufacturing Processes** University of Massachusetts Lowell Rutgers, The State University of New Jersey	The goal of these projects is to develop a process simulation and modeling platform for integrated pharmaceutical manufacturing processes. The tools developed will be used to facilitate the risk assessment of manufacturing processes and control strategies and to identify critical material and process attributes through sensitivity analysis. The results will advance the understanding of how raw material attributes and process parameters affect quality of the final drug product.	5	3,4
2014	**Establishing Specifications to Assure the Quality of the Heparin Supply Chain** G. Ronzoni Institute for Chemical and Biochemical Research	The objective of this contract is to establish specifications for a key intermediate in the heparin supply chain that currently has no defined properties. The impact of this work will be to establish crude heparin as an intermediate which can be monitored for quality. The outcome will allow FDA to check heparin quality earlier in the supply chain thereby preventing contaminated material from reaching the active pharmaceutical ingredient purification process and thus help ensure the quality of generic heparin products.	2	3

Fiscal Year	Project Title and Grantee(s)	Project Description	GDUFA Priority[19]	FDA Priority[15]
2013	Development of In Vivo Predictive Dissolution Method for Orally Inhaled Drug Products University of Bath, University of Florida, and Virginia Commonwealth University	The goal of these grants is to develop an in vitro dissolution method for orally-inhaled drug products (OIDPs) that will be capable of predicting in vivo dissolution of drugs that are administered via the inhalation route. The outcome of the project will aid in development of a tool that could be used for formulation development and optimization as well as product quality control. The multiple awards allow the evaluation of alternative approaches.	3, 4	3
2013	Systematic Evaluation of Excipient Effects on the Efficacy of Metered Dose Inhaler Products Cirrus Pharmaceuticals	The goal of this grant is to investigate the effect of excipient concentrations on the aerosolization performance of typical hydroflouroalkane (HFA) - based metered dose inhaler (MDI) formulations, as well as to evaluate the sensitivity of in vitro methods in detecting excipient concentration changes. Success would support allowing differences in inactive ingredients in generic MDI products.	3, 4	3
2013	Investigate the Sensitivity of Pharmacokinetics in Detecting Differences in Physicochemical Properties of the Active in Suspension Nasal Products for Local Action University of Florida	The contract will investigate the effect of physicochemical properties of the active in suspension nasal drug product for local action including, but not limited to, particle size, morphic form and solvation state on the pharmacokinetic behavior of the drug product. This project could lead to a new bioequivalence approach for nasal spray suspension products.	3, 4	2
2013	Effect of Different Protective Packaging Configurations on Stability of Fluticasone Propionate Capsules for Inhalation University of Florida	This contract comprises packaging of the fluticasone propionate capsules using various packaging materials to determine the optimum packaging that will ensure stability of this drug product during shipment and the intended period of use in a research study. This contract supports previously awarded research activities on inhalation bioequivalence.	3, 4	3

Fiscal Year	Project Title and Grantee(s)	Project Description	GDUFA Priority[19]	FDA Priority[15]
2013	In Vitro Release Tests for Transdermal Drug Delivery Systems University of Cincinnati and University of Maryland	The goal of these studies is to develop and characterize in vitro methods for evaluating the comparative safety of drug release from generic transdermal systems when exposed to levels of heat relevant to product use (e.g., hot showers, saunas, heating blankets). A central focus of this work is the in vitro – in vivo correlation (IVIVC), which characterizes the degree to which results measured in the laboratory accurately predict the bioavailability of drug when applied to living humans. The University of Maryland award includes in vivo studies while the University of Cincinnati award focuses on computational modeling of heat effects.	2, 3, 4, 5	3, 4
2013	In Vitro Release Tests for Topical Dermatological Products Joanneum Research and University of Maryland	The goal of these studies is to develop and characterize surrogate measures of clinical performance for topical semisolid drug products (e.g., creams, ointments, gels) by measuring comparative bioavailability and bioequivalence. A central focus is to determine the degree to which results measured by surrogate methods accurately predict the bioavailability and/or bioequivalence of drug delivery when applied to living humans. The University of Maryland award is a 5 year award investigating multiple potential surrogate methods with a range of products. The Joanneum Research award investigates the potential for in vivo human Open Flow Microperfusion studies to evaluate the bioequivalence of topical products.	2, 3, 4	3, 4
2013	Correlation of Mesalamine Pharmacokinetics with Local Availability University of Michigan	This contract is to establish quantitative correlation of plasma PK data with local gastrointestinal (GI) concentration and to improve physiologically-based models for colon absorption. Results could lead to new approaches to determining the bioequivalence of locally acting GI drug products and improved understanding of colon absorption from modified release products.	3	2, 3

Fiscal Year	Project Title and Grantee(s)	Project Description	GDUFA Priority[19]	FDA Priority[15]
2013	In Vitro and In Vivo Correlations of Ocular Implants University of Colorado Denver and Auritec Pharmaceuticals, Inc.	The purpose of these grants is to investigate in vitro-in vivo correlations of ophthalmic intravitreal implants. In each award, an in vitro dissolution test that correlates with in vivo ocular absorption will be investigated and compared to an animal model. The two awards will study different drugs and could help develop in vitro bioequivalence methods or improved release tests for this product category.	2, 3	2, 3
2013	In vitro-In vivo Correlations of Parenteral Microsphere Drug Products University of Connecticut Storrs and University of Michigan	The purpose of these grants is to investigate in vitro-in vivo correlations of parenteral microspheres. An in vitro dissolution test which correlates with in vivo absorption will be investigated. The two awards will study different drugs and could lead to better guidance for industry on the development of in vitro release tests for parenteral microspheres. Better in vitro release tests will also accelerate product development of generic microsphere formulations.	2	2, 3
2013	Prediction of In Vivo Performance for Oral Solid Dosage Forms University of Michigan	The purpose of this contract is to improve prediction of in vivo performance of oral solid dosage forms. The scope includes modeling of GI fluid hydrodynamics, sampling of GI tract fluids composition and pH, novel dissolution methods and in vivo PK studies to validate model predictions.	3, 5	2, 3, 5
2013	Collection of Dose Adjustment and Therapeutic Monitoring Data for Narrow Therapeutic Index (NTI) Drug Classification Duke University and Johns Hopkins University	The objective of this grant is to collect drug dose adjustment and therapeutic monitoring data in patients to aid NTI classification. The two awards will use different medical record databases.	5	1, 2, 5

Fiscal Year	Project Title and Grantee(s)	Project Description	GDUFA Priority[19]	FDA Priority[15]
2013	Bioequivalence of Generic Bupropion Washington University	The purpose of this multi-year grant is to (1) demonstrate bioequivalence between generic and brand name bupropion HCl modified release products with different release patterns at steady state in patients, and (2) evaluate whether patients can perceive the difference in release pattern and whether they experience lack of efficacy or increased adverse events after they are switched between each treatment. This grant (along with the two following awards) is part of a broader effort to better understand the root cause of recent problems with bioequivalence of bupropion.	1	2
2013	Investigation of Inequivalence of Bupropion Hydrochloride Extended Release Tablets: In Vitro Metabolism Quantification University of Michigan	The objective of this contract is to conduct detailed in vitro metabolism studies on bupropion that will study the enzymes involved in bupropion metabolism as well as the enzyme kinetics to provide data for further investigation of the inequivalence bupropion HCl extended release product.	1	3
2013	Pharmacokinetic Study of Bupropion Hydrochloride Products with Different Release Patterns University of Michigan	The objectives of this contract are to conduct healthy subject pharmacokinetic studies of bupropion HCl modified release products with different release patterns and different doses. This will help FDA understand how the release pattern of bupropion HCl products and the genotype of the metabolic enzyme may affect bioequivalence conclusions across different dose strengths within one product line due to the saturation of intestinal metabolism.	1	2

Fiscal Year	Project Title and Grantee(s)	Project Description	GDUFA Priority[19]	FDA Priority[15]
2013	Evaluation of Drug Product Formulation and In-Vitro Performance Characteristics Related to Abuse-Deterrence for Solid Oral Dosage Forms of Opioids National Institute for Pharmaceutical Technology and Education	The contract will investigate the relationship between the physicochemical properties of drug products, including the active ingredients, excipients, composition, and manufacturing technologies, and how these drug products are manipulated to extract the active ingredient for putative abuse. This investigation will employ various mechanical and chemical manipulation techniques commonly used by abusers to extract the active ingredient from the drug product and couple these with in-vitro characterization techniques. The goal is to have a better understanding of how material properties of excipients impact abuse-deterrent properties. This work will inform future FDA guidance on the evaluation of abuse-deterrent formulations in ANDAs.	1	3
2013	Postmarketing Surveillance of Generic Drug Usage and Substitution Patterns Brigham and Women's Hospital and University of Maryland Baltimore	The purpose of these grants are to evaluate existing tools and to develop new methods to proactively monitor the drug safety, efficacy, usage, and substitution patterns of recently approved generic drugs whose approval was controversial and to evaluate if controversy during the approval process affects their acceptance by physicians and patients. The results will help FDA develop surveillance plans for future generic drug approvals	1	8
2013	Evaluation of Clinical and Safety Outcomes Associated with Conversion from Brand-Name to Generic Tacrolimus Products in High Risk Transplant Recipients University of Cincinnati	The objectives of this contract are to monitor the tacrolimus trough concentration in high immunologic risk patient populations after switching of all marketed tacrolimus capsule products and to evaluate the necessity of therapeutic monitoring following each substitution. This study will evaluate clinical and safety outcomes among higher risk transplant recipients whose tacrolimus was converted from the brand-name formulation to multiple generic formulations. Results from this project will support generic substitution in all transplant patients.	1	2

Fiscal Year	Project Title and Grantee(s)	Project Description	GDUFA Priority[19]	FDA Priority[15]
2013	Development of Bio-Relevant In-Vitro Assay to Determine Labile Iron in the Parenteral Iron Complex Product Albany College of Pharmacy	The objective of this grant is to evaluate various in-vitro methods of determining labile iron and develop a bio-relevant in-vitro method to predict the amount of non-transferrin bound iron in vivo. Results from this project will improve in vitro release tests for iron complexes and allow FDA to provide consistent guidance to ANDA sponsors on this topic.	5	1, 2
2013	Evaluation of Dissolution Methods for Complex Parenteral Dosage Forms University of Kentucky and ZoneOne Pharma, Inc	The objective of these grants is to evaluate current in vitro release methods for complex parenteral dosage forms and analyze their capabilities to detect formulation differences and predict in-vivo performance and method robustness. The two awards will study different liposomal formulations. Better in vitro release methods will accelerate product development of generic liposomal formulations.	2	3
2013	Heparin Induced Thrombocytopenia (HIT) Consortium University of North Carolina, Chapel Hill	The objective of this grant is to identify which components of the heparin drug mixtures have the propensity to cause heparin induced thrombocytopenia (HIT) pathogenesis. The results of the study will identify heparin components that enhance HIT propensity which could potentially be minimized in heparin manufacturing. The outcome is to improve the safety profile of generic heparin.	1	1, 3

2. Recent intramural accomplishments relevant to the development of safe and effective generic drugs

Research Accomplishments by FDA Researchers That Further Generic Drug Development

Accomplishment	Significance	GDUFA Priority[19]	FDA Priority[15]
Ensured the quality of the generic version of low-molecular-weight heparins. FDA investigators developed "gatekeeper assays," based on nuclear magnetic resonance and high-performance chromatography, to ensure the quality of low molecular-weight heparins, which are widely used as anticoagulants in patients with cardiovascular conditions. Based on these gatekeeper tests, the researchers also conducted a systematic comparison of innovator and generic versions of enoxaparin to demonstrate the usefulness of these assays for ensuring quality of generic versions. Ye, H., Toby, T. K., Sommers, C. D., Ghasriani, H., Trehy, M. L., Ye, W., ... & Keire, D. A. (2013). Characterization of currently marketed heparin products: Key tests for LMWH quality assurance. *Journal of pharmaceutical and biomedical analysis*, 85, 99-107.	Heparin contamination has been linked to an estimated 81 fatalities. Quality control of this widely used product is essential given the complex supply chain of the raw material used in its production.	2, 5	3
Determined critical quality attributes of an ophthalmic emulsion. FDA researchers made use of a quality-by-design approach to ascertain the effect of a set of formulation and process variables on critical quality attributes of cyclosporine emulsion (Restasis), for which no generics are available. Rahman, Z., Xu, X., Katragadda, U., Krishnaiah, Y. S., Yu, L., & Khan, M. A. (2014). Quality by Design Approach for Understanding the Critical Quality Attributes of Cyclosporine Ophthalmic Emulsion. *Molecular pharmaceutics*, 11(3), 787-799.	The results of this study laid the groundwork for a procedure that determined the bioequivalence of generic versions of this widely-used product.	2, 3	3, 4

Accomplishment	Significance	GDUFA Priority[19]	FDA Priority[15]
Detected harmful adulterants. FDA researchers compared different analytical techniques (thermal analysis, X-ray diffraction, Fourier transform infrared (FT-IR), FT-Raman, and near-infrared spectroscopy) for their ability to detect a range of melamine levels in gelatin, a common component of drug capsules. They found that analyzed appropriately, near-infrared spectroscopy data yielded the most accurate model for quantifying melamine contamination. Cantor, S. L., Gupta, A., & Khan, M. A. (2014). Analytical Methods for the Evaluation of Melamine Contamination. *Journal of pharmaceutical sciences*, 103(2), 539-544.	Drug adulteration or contamination with melamine is a potential public health concern as it is a known nephrotoxin. FDA researchers provided useful experimental information for regulators seeking to prevent melamine contamination in the pharmaceutical supply chain.	5	1
Developed chemometric methods for analyzing a drug in a solid dispersion formulation. FDA researchers developed a chemometric approach based on X-ray diffraction for quantifying the percentage of crystalline tacrolimus, an important immunosuppressive agent, in a solid dispersion formulation of the drug. Siddiqui, A., Rahman, Z., Bykadi, S., & Khan, M. A. (2014). Chemometric Methods for the Quantification of Crystalline Tacrolimus in Solid Dispersion by Powder X-Ray Diffractrometry. *Journal of pharmaceutical sciences*. (E-pub ahead of print)	Solid dispersion formulations, though critical for bioavailablity, are somewhat unstable and this approach may have wide applicability in ensuring the quality of innovator and generic drugs.	5	3, 4
Pharmaceutically characterized a colloidal drug product. FDA researchers conducted a systematic study of the nature and stability of colloidal iron sucrose using a novel analytical study based on gel permeation chromatography and found that the components were thermodynamically stable. Rakhi B. Shah, Yongsheng, Yang, Mansoor A.Khan, Andre Raw, Lawrence X. Yu, Patrick J. Faustino, 2014**.** Pharmaceutical Characterization and thermodynamic stability assessment of a colloidal iron drug product: Iron sucrose. Int .J. Pharm. 464(1-2), 46-52.	Colloidal iron sucrose is used to treat patients who are anemic due to dialysis and represents a class of novel and complex products for which new approaches must be validated to ensure product quality.	2, 5	3

Accomplishment	Significance	GDUFA Priority[19]	FDA Priority[15]
Ensured the quality of a topical drug product. FDA researchers used a design-of-experiments approach to investigate the effect of manufacturing process variability on structural and functional characteristics of generic equivalents of a topical skin cream drug product, Zovirax (acyclovir). Yellela S.R. Krishnaiah, Xiaoming Xu, Ziyaur Rahman, Yang Yang, Usha Katragadda, Robert Lionberger, John R. Peters, Kathleen Uhl, Mansoor A. Khan, 2014. Development of Performance Matrix of generic equivalence of acyclovir topical creams. Int. J. Pharm, 475 (1-2), 110-122.	Topically-applied skin products present special challenges for determining bioequievalence. This work outlined an approach for testing these products and confirmed the feasibility of manufacturing generic equivalents of acyclovir.	2, 3, 4	3, 4
Conducted a systematic study of bioequivalence submissions. FDA conducted a survey of 4028 bioequivalence submissions over a 10-year period (2001–2011) to identify the most commonly occurring bioanalytical deficiencies and found that the majority of the deficiencies involved bioanalytical method validation, with the most numerous deficiencies related to demonstration of long-term stability. Williamson, L. N., Conner, D. P., Stier, E. M., & Davit, B. M. (2014). Common bioanalytical deficiencies with bioequivalence submissions in Abbreviated New Drug Applications. *Bioanalysis*, 6(4), 441-445.	This survey may help pharmaceutical sponsors eliminate what are often avoidable problems with applications for generic drugs.	2, 3, 4, 5,	2, 3
Assessed the quality of drugs that act locally in the GI tract. FDA investigators developed an in vitro approach that can be used in lieu of pharmacokinetic or clinical studies to determine the bioequivalence of lanthanum carbonate chewable tablets. Yang, Y., Bykadi, S., Carlin, A. S., Shah, R. B., Yu, L. X., & Khan, M. A. (2013). Comparative evaluation of the in vitro efficacy of lanthanum carbonate chewable tablets. *Journal of pharmaceutical sciences*, 102(4), 1370-1381.	This work identifies in vitro approaches that can be used to compare generic and innovator drugs that act locally in the gastrointestinal tract, drugs for which traditional pharmacokinetic studies may not be informative.	3, 5	3

Accomplishment	Significance	GDUFA Priority[19]	FDA Priority[15]
Determined the equivalence of particle sizes in orally-inhaled drug products. FDA investigators developed a modified statistical approach for comparing the particle size distribution of orally-inhaled drug products. Weber, B., Hochhaus, G., Adams, W., Lionberger, R., Li, B., Tsong, Y., & Lee, S. L. (2013). A stability analysis of a modified version of the chi-square ratio statistic: implications for equivalence testing of aerodynamic particle size distribution. *The AAPS journal*, 15(1), 1-9.	Demonstration of equivalent particle size distribution for orally-inhaled drug products is one of the key in vitro tests supporting equivalence between generic and innovator versions. The new statistical approach may be more robust than the one in current use.	5	3, 4
Determined the reasons for "for cause" inspections. FDA surveyed its databases to identify the common reasons that FDA conducts "for-cause" inspections on clinical, analytical, and dissolution study sites associated with bioequivalence studies of generic drug products and identified common reasons for requests for "for cause" inspections. Li, B. V., Davit, B. M., Lee, C. H., Pabba, S. K., Mahadevan, C., Caramenico, H. T., ... & Conner, D. P. (2013). Common Reasons for "For-Cause" Inspections in Bioequivalence Studies Submitted to the Food and Drug Administration. *The AAPS journal,* 15(1), 10-14.	The information resulting from this survey may help the pharmaceutical industry understand the root causes of compliance failures in BE studies and improve compliance with FDA's regulations, thereby facilitating more rapid approval of safe and effective generic drugs.	1	1
Evaluated sampling duration in pharmacokinetic studies. FDA conducted a simulation study to investigate the impact of sampling duration in clinical studies of bioequivalence of drugs with slow-sustained-release formulations. El-tahtawy, A., Harrison, F., Zirkelbach, J. F., & Jackson, A. J. (2012). Bioequivalence of long half-life drugs—Informative sampling determination—Using truncated area in parallel-designed studies for slow sustained-release formulations. *Journal of pharmaceutical sciences*, 101(11), 4337-4346.	The simulation study provided insights as to the needed duration of sampling for this class of drugs and may help drug developers avoid unnecessarily prolonged clinical bioequivalence studies.	2, 4	2, 5

Accomplishment	Significance	GDUFA Priority[19]	FDA Priority[15]
Characterized complex peptide products. FDA researchers developed a method for identifying protein fragments in complex peptide/protein products based on mass spectroscopy approaches. Gucinski, A. C., & Boyne, M. T. (2014). Identification of site-specific heterogeneity in peptide drugs using intact mass spectrometry with electron transfer dissociation. Rapid Communications in Mass Spectrometry, 28(15), 1757-1763.	The selectivity and sensitivity of the new method improves the ability of regulators to identify impurities not previously observed using the established methods and presents an opportunity to better understand the composition of complex peptide drug products.	2	3
Measured the serum concentration of a drug when other drugs are present. An analytical method combining fast liquid chromatography, heated electrospray ionization, and mass spectrometry was developed for detection of a widely used anti-epileptic in patients treated with other drugs. Wong, J. M., Jones, J. W., Jiang, W., Polli, J. E., & Kane, M. A. (2014). Quantification of lamotrigine in patient plasma utilizing a fast liquid chromatography-tandem mass spectrometry method with backflush technology. *Therapeutic drug monitoring*. [Epub ahead of print]	Neurologists and patients raised concerns recently regarding the bioequivalence of generic versions of Lamictal. This assay will permit required bioequivalence studies in epileptic patients treated with other medications.	1, 4	2
Identified quality attributes of drug products delivered using metered dose inhalers. FDA researchers conducted a series of in vitro tests to compare two classes of metered dose inhalers and identified a combination of characterisitics that could reliably differentiate the inhalers tested. Doub, W. H., Shah, V., Limb, S., Guo, C., Liu, X., & Ngo, D. (2014). Developing an In Vitro Understanding of Patient Experience with Hydrofluoroalkane-Metered Dose Inhalers. Journal of pharmaceutical sciences, 103(11), 3648-3656.	FDA's post-market surveillance system has identified many complaints regarding drug products delivered by metered dose inhalers. This research identified laboratory measures that were correlated with patient experience and show promise for improved evaluation of these products.	2	3, 4

Accomplishment	Significance	GDUFA Priority[19]	FDA Priority[15]
Measured leakage from transdermal patches. FDA researchers developed a method for measuring cold flow (adhesive oozing out from under the backing of transdermal drug delivery systems and interfering with drug absorption) using steromicroscopic imaging. Krishnaiah YS, Yang Y, Hunt RL, Khan, MA, Cold flow of estradiol transdermal systems: Influence of drug loss on the in vitro flux and drug transfer across human epidermis. Int Journal Pharmaceutics, 2014 Dec 30;477(1-2):73-80.	The new method will permit quantification of this phenomenon to ensure the quality of a rapidly-growing class of drug products.	3	3

ii. Adopting Advances in Regulatory Science to support the Goals of GDUFA

1. Guidance documents that support the development of safe and effective generic drugs

As drug products become more complex and rely on a variety of formulations and delivery mechanisms, determining the evidence needed to support approval of generic drug products becomes increasingly challenging. To realize the intent of GDUFA, FDA is actively engaged in developing clear guidance for industry that will accelerate generic drug development. Complex generic products for which FDA has recently issued guidance include fluticasone propionoate-salmeterol xinafoate formulated as a dry powder for inhalation; doxorubicin, amphotericin B, daunorubicin citrate, and verteporfin in liposomal formulations; cyclosporine in an opthalmic emulsion; lidocaine to be delivered via a topical patch; iron sucrose, a colloid drug product that is delivered parenterally; and albuterol sulfate formulated to be delivered with a metered dose inhaler.[20]

Examples of Recently Issued Guidances That Further Generic Drug Development

Guidance	Date	Significance
Abbreviated New Drug Applications: Stability Testing of Drug Substances and Products; Questions and Answers	May 2014	Answers questions obtained from public comments to a previous draft guidance, *ANDAs: Stability Testing of Drug Substances and Products*
Draft Guidance for Industry on Immunogenicity-Related Considerations for the Approval of Low Molecular Weight Heparin for New Drug Applications and Abbreviated New Drug Applications	April 2014	Discusses immunogenicity-related approval considerations for low molecular weight heparin products, including recommendations for meeting the requirement for active ingredient sameness in applications for generic products.
Draft Guidance for Industry on Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application	December 2013	Describes how to meet the bioequivalence requirements for generic orally- and non-orally administered drug products for which reliance on systemic exposure measures is appropriate.
Draft Guidance for Industry on Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules	December 2013	Provides recommendations for generic equivalents of innovator drugs concerning size, shape, and attributes like coating, disintegration time, and other physical properties that, although not relevant to pharmaceutic or therapeutic equivalence, may affect compliance or lead to medication errors

[20] In FY 2013, a total of 49 new product-specific bioequivalence guidances were posted, and 28 revisions were made to guidances already posted. Corresponding numbers for FY 2014 were 78 and 55, respectively.

2. Workshops and meetings to advance the goals of GDUFA

Examples of Recent Public Workshops and Workshops for Purposes of Training FDA Staff on Topics in Generic Drug Development

Event	Date	Significance
Seminar and round table discussion: Mechanistic Approach to In Vivo Predictive Dissolution Methodology Development and Selection	October 21, 2014	This workshop for FDA staff focused on the mechanistic approaches to in vivo predictive dissolution.
Workshop: Statistics in In Vitro and In Vivo Bioequivalence	September 25-26, 2014	This workshop for FDA staff covered the major issues, theoretical basis, available methodologies, remaining challenges, and future directions in the in vitro and in vivo testing for generic drug products. Approximately 110 FDA employees attended the training on site or remotely.
Generic Drug User Fee Amendments of 2012; Regulatory Science Initiatives Part 15 Public Meeting	June 2013	This is a requirement under GDUFA to solicit input from industry and other stakeholders to develop an annual list of regulatory science initiatives.
Questioning the bioequivalence standards for antiepileptic drugs: implications for regulation of narrow therapeutic index drugs	May 2014	This workshop discussed the effectiveness of current regulatory standards governing generic drug approval, including the most appropriate and acceptable approach for assessing generic bioequivalence to ensure therapeutic equivalence. The focus was on anti-epileptic bioequivalence in epilepsy patients.
Generic Drug User Fee Amendments of 2012; Regulatory Science Initiatives Part 15 Public Meeting	May 2014	This is a requirement under GDUFA to solicit input from industry and other stakeholders to develop an annual list of regulatory science initiatives.

III. Advancing and Adopting Regulatory Science Relevant to Biosimilars

The Biologics Price Competition and Innovation *(*BPCI) Act of 2009, enacted under the Patient Protection and Affordable Care Act (Public Law 111-148) in 2010, created an abbreviated licensure pathway for biological products demonstrated to be biosimilar to, or interchangeable with, a US-licensed reference product. Biosimilarity is defined in the BPCI Act to mean "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product." The Biosimilar User Fee Act of 2012 (BsUFA), enacted as part of FDASIA, authorizes FDA to assess and collect user fees to expedite FDA's regulatory review of biosimilar applications.

The first recombinant protein product, human insulin, was approved by the FDA in 1982 and the first monoclonal antibody, muromonab, a treatment for acute transplant rejection, was approved in 1986. Advances in analytical sciences enable some protein products to be extensively characterized with respect to their physico-chemical and biological properties, such as higher order structures and functional characteristics. These analytical methodologies have increasingly improved the ability to identify and characterize not only the drug substance of a protein product but also excipients and product- and process-related impurities. The FDA, therefore, has gained extensive experience with protein therapeutics, including monoclonal antibodies, which has informed the development of initial guidance documents for biosimilars.

Effective implementation of the new approval pathway for biosimilars requires the agency to provide science-based regulatory advice to sponsors related to the evidence needed to establish biosimilarity. The 2012 FDA Draft Guidance, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, notes that because of the potential uniqueness of each development program "FDA will ordinarily provide feedback on a case-by-case basis on the components of a development program for a proposed product." There are opportunities to advance the regulatory science in areas that can bring added clarity to the development process and certainty to regulatory decisions. These include extending our understanding of the relationship between a product's structural attributes and its clinical performance, more fully understanding the effect of manufacturing conditions on critical quality attributes, improved methods for immunogenicity assessment, developing relevant potency assays, predicting drug-biologic interactions, developing sensitive and reproducible product-specific pharmacodynamic biomarkers, enhancing pharmacokinetic assessments for clinical pharmacology biosimilarity studies and refining statistical approaches critical to a determination of analytical similarity to support a demonstration of "highly similar." As the scientific and regulatory knowledge base grows, analysis of accumulated data improve understanding of the predictive value of clinical

pharmacology tools, thereby offering the possibility of easing the regulatory burden by reducing the need for full-blown clinical trials.

i. Progress in Advancing Regulatory Science Relevant to Biosimilars: Selected Examples

Protein therapeutic products have been under regulatory review for over 30 years, FDA scientists have a longstanding engagement in research efforts to advance the science needed for their effective regulatory evaluation. These include research on methods for comparing structural and functional attributes of protein therapeutics from different sources. Furthering the regulatory science relevant to the manufacture, structural analysis, assessment of biologic activity and clinical performance is relevant to both innovator biologic products and to biosimilars. Examples presented are relevant to Priority areas I through V of the Strategic Plan for Regulatory Science.

Notably, a number of the examples below involve collaboration with international regulators, academic, and industry experts, often through working groups organized by scientific societies. As regulatory science progresses, biosimilars development and review will undergo refinement as knowledge gained from pre- and post-market review experience is combined with scientific advancements demonstrated with sufficient rigor to support regulatory decision-making.

1. Examples of advances in regulatory science related to biologics organized by priority area (FY 2013-2014)

Examples of Advances in Regulatory Science related to Biologics Organized by Priority Area (FY 2013-2014)

Accomplishment	Significance
Priority I - Modernize Toxicology to Enhance Product Safety	
Trastuzumab is a monoclonal antibody that improves outcomes in for women with HER-2 positive breast cancer, but it may adversely affect the heart. FDA Scientists explored the mechanism of trastuzumab cardiac toxicity in a mouse model. Trastuzumab significantly altered the expression of myocardial genes essential for DNA repair, cardiac and mitochondrial functions, impaired cardiac function and altered cardiac biomarkers. Elzarrad MK, et al. Trastuzumab alters the expression of genes essential for cardiac function and induces ultrastructural changes of cardiomyocytes in mice. *PLoS One* 2013 Nov 8;8(11):e79543.	These findings address the mechanism of trastuzumab cardiac toxicity. Observed changes in cardiac proteins provide a basis for additional studies to assess their potential as biomarkers of cardiac toxicity.

Accomplishment	Significance
Pre-clinical testing of the safety and efficacy of protein biologic products in humans is challenging, because unwanted immune reactions, one of the primary factors that can affect safety and efficacy, cannot be adequately evaluated in an animal model. FDA Scientists established a mouse model with an engrafted human immune system that is being evaluated for its ability to predict immune responses in humans. Howard KE et al. Humanized Mice: A New Animal Model for Risk Assessment of Biologics. *The Toxicologist*. 2013 Mar; 132(1):385 Howard KE et al. Assessing Safety and Efficacy of Anti-CD20 Biologics in Human Immune System Mice. *The Toxicologist*, 2014 Mar; 138(1):579.	The mouse model mimicked human immune responses to a biologic drug. The humanized mouse model may prove a valuable pre-clinical tool for predicting and understanding unwanted human immune reactions to biologic therapeutics.
The FDA co-sponsored a workshop to discuss methodologies to assess potential drug-drug interactions involving therapeutic proteins (TP-DDI). A collaborative workgroup with industry and the FDA members discussed the use of *in vitro* systems to evaluate potential drug-drug interactions involving therapeutic proteins that affect inflammation. The workgroup shared and analyzed data from a number of *in vitro* studies to assess several factors, including variability and predictive value. Evers, R., Dallas, S., Dickmann, L. J., Fahmi, O. A., Kenny, J. R., Kraynov, E., ... & Zhang, L. (2013). Critical Review of Preclinical Approaches to Investigate Cytochrome P450–Mediated Therapeutic Protein Drug-Drug Interactions and Recommendations for Best Practices: A White Paper. *Drug Metabolism and Disposition*, *41*(9), 1598-1609.	Work group concluded that evaluation of drug-drug interactions involving therapeutic proteins is still best done in clinical studies; pre-clinical models may be useful for mechanistic studies; and improvements in *in vitro* systems are needed.
Priority II - Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes.	
FDA Scientists participated in a special session at the 2013 American Association of Pharmaceutical Scientists-National Biotechnology Conference which focused on the 2013 FDA draft guidance on immunogenicity. The discussion included a broad range of scientists with expertise in the development of biologics. Parenky, A., Myler, H., Amaravadi, L., Bechtold-Peters, K., Rosenberg, A., Kirshner, S., & Quarmby, V. (2014). New FDA Draft Guidance on Immunogenicity. The AAPS journal, 16(3), 499-503.	The published conference summary makes a valuable contribution to the ongoing scientific discussions around critical aspects of immunogenicity including scientific knowledge gaps.

Accomplishment	Significance
Although enzyme replacement therapy (ERT) is a highly effective therapy, CRIM-negative (CN) infantile Pompe disease (IPD) patients typically mount a strong immune response which abrogates the efficacy of ERT, resulting in clinical decline and death. FDA researchers collaborated in a study that demonstrated that immune tolerance induction prevents or diminishes the development of antibody titers, resulting in a better clinical outcome compared to CN IPD patients treated with ERT monotherapy. Banugaria, S. G., Prater, S. N., Patel, T. T., DeArmey, S. M., Milleson, C., Sheets, K. B., ... & Kishnani, P. S. (2013). Algorithm for the early diagnosis and treatment of patients with Pompe disease: a step towards improving the efficacy of ERT. PloS one, 8(6), e67052.	The research suggests that induction of immune tolerance can be safe and may improve efficacy of enzyme replacement therapy for a severe inherited disease.
Immunogenicity is an important consequence of biologic drugs. FDA scientists participated in the Therapeutic Protein Immunogenicity Focus Group of the American Association of Pharmaceutical Scientists to consider recommendations that would foster a more unified approach to assessing immunogenicity. Shankar, G., Arkin, S., Cocea, L., Devanarayan, V., Kirshner, S., Kromminga, A., ... & Yim, S. (2014). Assessment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and Peptides—Harmonized Terminology and Tactical Recommendations. The AAPS journal, 1-16.	The focus group proposals included standard terms for describing and analyzing immunogenicity data and approaches to data analysis and data presentation.
For many small molecule drugs, studies in patients with reduced liver function are necessary, since this condition can greatly alter the circulating levels of drugs, thereby affecting their safety or effectiveness. FDA scientists conducted a retrospective review of information on 91 therapeutic proteins to better understand whether dedicated pharmacokinetic studies in patients with liver impairment were conducted, and whether data to better estimate the effect of hepatic impairment on PK for protein therapeutics is available. Yang J, et al. Are Hepatic Impairment Studies Necessary for Therapeutic Proteins? *Clin Ther* , 2013 Sep;35(9):1444-51.	No dedicated pharmacokinetics trials for TPs in patients with hepatic impairment have been conducted. It is important to continue collecting pharmacokinetic data of therapeutic proteins in patients with hepatic impairment and use population pharmacokinetic analyses to evaluate the effect of hepatic impairment on the pharmacokinetics of TP.

Accomplishment	Significance
There has been little research on the physiological basis for antibody drug adsorption. FDA Scientist proposed a quantitative model to describe the absorption process for monoclonal antibody (mAb) following subcutaneous or intramuscular administration. The modeling results suggested lymphatic flow was a major route of mAb delivery. Zhao, L., Ji, P., Li, Z., Roy, P., & Sahajwalla, C. G. (2013). The antibody drug absorption following subcutaneous or intramuscular administration and its mathematical description by coupling physiologically based absorption process with the conventional compartment pharmacokinetic model. The Journal of Clinical Pharmacology, 53(3), 314-325.	The model provides insight in quantitatively understanding the absorption process of monoclonal antibody drugs. Refinements to the modeling approach could be useful during the development process for biologics.
The FDA co-sponsored a workshop to discuss methodologies to assess potential drug-drug interactions involving therapeutic proteins (TP-DDI). A collaborative workgroup with industry and FDA members discussed the utility of population pharmacokinetic (PK)-based TP-DDI assessment including study designs, data analysis methods, and implementation strategy with focuses on population PK approach for both exploratory and confirmatory assessments, importance of data quality, implementation strategy; and potential regulatory implications. Advantages and limitations of the approach are also discussed Chow, A. T., Earp, J. C., Gupta, M., Hanley, W., Hu, C., Wang, D. D., ... & Zhu, M. (2014). Utility of population pharmacokinetic modeling in the assessment of therapeutic protein-drug interactions. The Journal of Clinical Pharmacology, 54(5), 593-601.	Workgroup concluded that: The population PK approach can be a viable tool for TP-DDI assessment and help overcome constraints in study designs for different therapeutic areas. Properly designed DDI studies can lead to the collection of high quality data that may support either exploratory and/or confirmatory analyses. With strategic planning and early interaction with regulatory authorities, application of population PK approach to DDI assessment may improve efficiency of drug development.
An anti-drug antibody (ADA) assay is one tool used to assess development of an immune response to a biologic drug. The presence of the biologic drug in the sample being measured may interfere with the accurate measurement of ADAs. In order to better understand the potential impact, FDA researchers surveyed of applications of biological products to understand the potential effect of circulating drugs on ADA assays. Wang YM, et al. A survey of applications of biological products for drug interference of immunogenicity assays *Pharm Res* 2012 Dec; 29(12):3384-92.	For a significant portion of biologics, peak circulating concentrations were high enough to potentially affect the ADA assay. Several strategies to mitigate this potential challenge in assessing immunogenicity were proposed.

Accomplishment	Significance
Priority III - Support New Approaches to Improve Product Manufacturing and Quality	
Controlling the quality of monoclonal antibodies used to treat cancer and other chronic diseases. Biologics pose formidable challenges in the area of product quality and manufacturing. FDA researchers used Design of Experiment and Process Analytic Technology (PAT) approaches to identify key parameters affecting glycoslylation of monoclonal antibodies, which is often a critical determinant of the anticancer activity of these molecules. Agarabi C, et al. Bioreactor Process Parameter Screening Utilizing a Plackett-Burman Design for a Model Monoclonal Antibody. *(Journal of Pharmaceutical Science* – (in press).	FDA researchers developed a systematic approach to controlling some of the key quality attributes of monoclonal antibodies, which are increasingly important as cancer therapeutics.
Production of monoclonal antibodies is done in cell culture. Manipulations to boost antibody production may lead to depletion of key amino acids critical for maintenance of the culture. FDA Scientists used advanced analytical techniques to map depletion of key ingredients in cell cultures that were producing monoclonal antibodies, and then used this information to develop a strategy for improving the culture performance. Read, E. K., Bradley, S. A., Smitka, T. A., Agarabi, C. D., Lute, S. C., & Brorson, K. A. (2013). Fermentanomics informed amino acid supplementation of an antibody producing mammalian cell culture. Biotechnology progress, 29(3), 745-753.	FDA scientists describe a strategy to monitor information on critical bioreactor ingredients, and then use the information to improve the performance of culture systems. The approach can increase production of therapeutic proteins while maintaining product quality.
Methods that boost therapeutic protein production in cell-based systems may also affect the product quality. FDA Scientists examined the effect of butyrate on the production rate of a therapeutic protein and also assessed functional properties of the protein and measured critical quality attributes, such as glycosylation. Madhavarao, C. N., Agarabi, C. D., Wong, L., Müller-Loennies, S., Braulke, T., Khan, M., ... & Johnson, G. R. (2014). Evaluation of butyrate-induced production of a mannose-6-phosphorylated therapeutic enzyme using parallel bioreactors. Biotechnology and applied biochemistry, 61(2), 184-192.	Additions to cell culture media can boost production of a target protein, but may also affect critical quality attributes that affect product stability, safety or efficacy. Evaluation of critical quality attributes should be incorporated into any evaluation of changes in bioreactor conditions.

Accomplishment	Significance
Therapeutic antibodies that are not stable in a liquid are freeze dried prior to storage and distribution. FDA Scientists used analytical tools to monitor and control several aspects of the freeze-drying process (process analytical technology) to study the impact on final product quality. Awotwe-Otoo, D., Agarabi, C., & Khan, M. A. (2014). An Integrated Process Analytical Technology (PAT) Approach to Monitoring the Effect of Supercooling on Lyophilization Product and Process Parameters of Model Monoclonal Antibody Formulations. Journal of pharmaceutical sciences.(E-pub ahead of print).	Dynamic monitoring and careful control of the freeze-drying process parameters can lead to more predictable and consistent quality for protein products.
Strategies and standards for the removal and inactivation of viruses during the purification of protein therapeutics produced in cell-based systems are important for final product safety and quality. FDA scientists have a long-standing focus on studying viral safety; their background work has contributed to recently released ASTM Standard, "Standard Practice for Process for Inactivation of Rodent Retrovirus by pH". Recent work has compared several technologies for viral removal and broadened understanding of the effect of changes in flow on viral filter performance. Miesegaes GR, et al. Viral clearance by flow-through mode ion exchange columns and membrane adsorbers. *Biotechnol Prog* 2014 Jan; 30(1):124-31.	This research provides scientific support for the introduction of newer disposable equipment for more flexible and cost-effective manufacture of biopharmaceuticals. By understanding technological gaps, like pausing associated virus breakthrough, virus filtration unit operations can be designed to avoid potential failure modes.
Priority IV - Ensure FDA Readiness to Evaluate Innovative Emerging Technologies	
Comparing the structure of the same complex protein therapeutic produced at different facilities with different production processes places an emphasis on analytical methods. FDA scientists applied several complementary analytical technologies to compare a US approved version of filgrastim with 3 foreign sourced versions that are not approved in the US. The project utilized mass spectrometry, circular dichroism and nuclear magnetic resonance spectroscopy along with an in vitro functional assay as orthogonal methods to characterize these proteins. Levy, M. J., Gucinski, A. C., Sommers, C. D., Ghasriani, H., Wang, B., Keire, D. A., & Boyne II, M. T. (2013). Analytical techniques and bioactivity assays to compare the structure and function of filgrastim (granulocyte-colony stimulating factor) therapeutics from different manufacturers. Analytical and bioanalytical chemistry, 1-9.	The application of multiple, complementary analytical approaches enabled the characterization of the critical structural and physical characteristics of a test protein drug and assessed the impact of structural changes on in vitro potency and efficacy.

Accomplishment	Significance
Therapeutic proteins undergo post-translational modifications during production such as glycosylation. Because glycosylation can affect safety and efficacy, the ability to characterize glycoproteins is critical. FDA scientists developed a new analytical method capable of identifying the number, location, and structure of glycosylation sites on glycoproteins, based advanced mass spectrometric technologies. Ye, H., Boyne, M. T., Buhse, L. F., & Hill, J. (2013). Direct approach for qualitative and quantitative characterization of glycoproteins using tandem mass tags and an LTQ orbitrap XL electron transfer dissociation hybrid mass spectrometer. Analytical chemistry, 85(3), 1531-1539.	An advanced mass spectrometric method was developed that can be used as a qualitative and quantitative technique for the direct characterization of glycoproteins. The method has applicability to the detection of counterfeit glycoprotein products.
FDA Scientists participated in a large, international, multisite study of methods to characterize glycoproteins. Using standard samples, the study participants applied different methods, assessing variability across laboratories and equipment. Leymarie, N., Griffin, P. J., Jonscher, K., Kolarich, D., Orlando, R., McComb, M., & Schulz, J. M. (2013). Interlaboratory study on differential analysis of protein glycosylation by mass spectrometry: the ABRF glycoprotein research multi-institutional study 2012. Molecular & Cellular Proteomics, 12(10), 2935-2951.	FDA scientists have a continued engagement in international methods development and validation activities. Multi-lab studies are important for determining the robustness of analytical methods.
FDA Scientists built and tested a deep ultraviolet Raman spectrometer to assess its ability to detect slight changes in the structure of several protein products. Information derived from the spectra of 3 formulated insulin products was able identify and distinguish the protein signals in the 3 formulated mixtures. Arzhantsev S, et al. Deep-Ultraviolet (UV) Resonance Raman Spectroscopy as a Tool for Quality Control of Formulated Therapeutic Proteins. *Appl Spectrosc* 2012 Nov; 66(11):1262-8.	Further development of resonance Raman spectroscopy may provide a tool for characterizing formulated protein therapeutics for quality control.
Analytical methods that can characterize therapeutic monoclonal antibodies and discern structural differences due to production changes, different manufacturer's process or to detect counterfeit products are evolving. FDA scientists applied a method of mass spectrometric analysis combined with targeted enzymatic cleavage to characterize two anti-CD20 monoclonal antibodies from different sources. Wang, B., Gucinski, A. C., Keire, D. A., Buhse, L. F., & Boyne II, M. T. (2013). Structural comparison of two anti-CD20 monoclonal antibody drug products using middle-down mass spectrometry. Analyst, 138(10), 3058-3065.	Mass spectrometric analytical methods coupled with selective cleavage can be a useful tool in distinguishing protein products from different manufacturers.

Accomplishment	Significance
Priority V–Harness diverse data through information sciences to improve health outcomes	
FDA researchers did a meta-analysis to look for a potential link between Guillain-Barré syndrome (GBS) and the use of the influenza A (H1N1) pandemic vaccine. The study concluded there were 1.6 excess cases of GBS per million people vaccinated, a modest risk consistent with previous estimates of GBS after seasonal influenza vaccination. Salmon, D. A., Proschan, M., Forshee, R., Gargiullo, P., Bleser, W., Burwen, D. R., & Lurie, N. (2013). Association between Guillain-Barré syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: a meta-analysis. The Lancet, 381(9876), 1461-1468.	The data support the conclusion that the benefits of the 2009 H1N1 vaccines outweighed the risks, which is an important reassurance for clinicians and consumers given the morbidity and mortality caused by the 2009 H1N1 influenza pandemic itself.
Priority VII–Facilitate development of medical countermeasures to protect against threats to U.S. and global health and security	
Researchers at FDA demonstrated an alternative and rapid way to produce a vaccine against a potential pandemic influenza virus. FDA researchers demonstrated that bacterially expressed recombinant HA1 immunogens, which contain a high percentage of functional oligomers, may provide an alternative H5N1 vaccine platform. When combined with the appropriate adjuvant, they are likely to generate high-affinity antibodies with the capacity to neutralize heterologous strains, control virus replication in the upper respiratory tract, and reduce virus transmission. Verma, S., Dimitrova, M., Munjal, A., Fontana, J., Crevar, C. J., Carter, D. M., & Golding, H. (2012). Oligomeric recombinant H5 HA1 vaccine produced in bacteria protects ferrets from homologous and heterologous wild-type H5N1 influenza challenge and controls viral loads better than subunit H5N1 vaccine by eliciting high-affinity antibodies. Journal of virology, 86(22), 12283-12293.	Safe and effective recombinant HA-based anti-H5N1 vaccines could provide an alternative to in vitro (chicken eggs) or in vivo (reverse genetics) techniques, thus saving several months of manufacturing time, since the HA gene of the newly circulating strain is available shortly after virus isolation. In addition, this was the first study to show the role of antibody avidity for the HA1 globular head domain in reducing viral loads in the upper respiratory tract.

ii. Progress in Adopting and Integrating Regulatory Science Relevant to Biosimilars

1. Workshops, public hearings, education and training

FDA provides extensive training opportunities for FDA personnel, including seminars with internal and external experts, which are addressed in the cross-cutting section on training (see Section V, II, 1). When a new regulatory requirement or pathway is established, training for staff on the regulatory and procedural aspects of implementation is given.

Progress in educating and getting input from the stakeholder community is accomplished in a number of venues. FDA personnel give numerous presentations at scientific meetings and academic seminars. While not detailed here, it is illustrative to note that the FDA/CDER Office of Biotechnology Products personnel gave nearly 100 external talks in 2013 and 2014. In addition to providing extensive materials on its website, the FDA sponsors workshops, public meetings, and webinars.

Examples of Recent Meetings and Workshops Devoted to Biosimilars

Activity	Date	Purpose
Clinical Investigator Course: Lecture[21] on Biosimilar Biological Products	November 4, 2014; November 13, 2013	This lecture was part of a two day clinical investigator course, which is available free on line. In addition to providing an overview of the biosimilar process, the lecture highlighted important considerations for designing appropriate clinical studies.
Biosimilar Biological Products FDA Basics Webinar[22]	August 8, 2014	This webinar provided a broad overview of biosimilars, including an introduction to biologic products, key definitions related to biosimilars, and an overview of the development and regulatory review process.
Therapeutic Protein-Drug Interaction Workshop[23]	June 6, 2012	The workshop gathered input from academics, industry and regulatory leaders on the value of in vitro/in vivo or population pharmacokinetic approach to therapeutic protein drug interaction assessment. Topics included study designs, data analysis methods, and implementation strategy with focuses on population PK approaches for both exploratory and confirmatory assessments.
Public Hearing:[24] Draft Guidance Documents Relating to the Development of Biosimilar Products	May 11, 2012	The hearing provided an opportunity for stakeholder input on draft biosimilar guidance documents. Presentations from a broad range of over 25 stakeholders including patient organizations, industry, academia, trade organizations and health care organizations.

2. Interactions with international regulators

Interactions with FDA's international regulatory counterparts are an important activity to advance adoption of new science into the regulatory processes. Regulators can promote global development of biosimilars, discuss general scientific review issues, discuss and share policy, experiences and best practices, and identify emerging issues. Two examples of international inter-agency cooperation are the following:

[21] www.fda.gov/downloads/Training/ClinicalInvestigatorTrainingCourse/UCM378510.pdf
[22] www.fda.gov/downloads/aboutfda/transparency/basics/ucm365448.pdf
[23] www.fda.gov/downloads/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm333444.pdf
[24] www.fda.gov/Drugs/NewsEvents/ucm265628.htm

EMA-FDA-Health Canada Biosimilar Cluster: FDA collaborates with the European Medicines Agency (EMA) and Health Canada to encourage alignment on scientific approaches to biosimilar product development. One example of a collaboration to share experiences and best practices to provide biological product developers assurance, when possible, that data developed for one regulatory authority could be acceptable to another regulatory authority is through the EMA-FDA-Health Canada Biosimilar Cluster. The Cluster began as collaboration between EMA and FDA in 2011. The members of this working group are representatives from EMA's Biosimilar Medicines Working Party and FDA's Biosimilar Implementation Committee. Health Canada joined the Cluster in July 2013. Japan's Pharmaceuticals and Medical Devices Agency (PMDA) will join the Cluster in March 2015.

International Pharmaceutical Regulators Forum (IPRF) for Biosimilars Working Group: The International Pharmaceutical Regulators Forum (IPRF) met in Osaka, Japan, on November 11 and 12, 2013, in connection with the International Conference on Harmonisation (ICH) Steering Committee meeting. At this meeting, the IPRF decided to establish a working group on biosimilars, which is chaired by the Korean Ministry of Food and Drug Safety. Several regulatory agencies will be involved, including FDA, EMA, and PMDA. The goal of this working group is to understand the legal requirements and constraints across many regulatory regions and determine the potential for alignment of scientific approaches.

3. Guidance development

One of the important outcomes of advancing regulatory science is its incorporation into guidance that can provide sponsors with recommendations intended to bring predictability to the development and review process. As a new regulatory pathway, development of the initial biosimilars guidance documents drew on the extensive experience of FDA reviewers and scientists with protein therapeutics, including monoclonal antibodies. In addition to guidance documents specifically targeted to biosimilar development, guidance documents related to innovator protein therapeutics may also be relevant to biosimilar products.

Recently Issued Guidances Focusing on Biosimilars

Category	Title	Date	Significance
Clinical/Medical; Chemistry, Manufacturing and Controls	Immunogenicity Assessment for Therapeutic Protein Products	August 13, 2014	The guidance makes recommendations for the adoption of a risk-based approach to evaluating and mitigating immune responses to adverse immunologically-related responses associated with therapeutic protein products that affect their safety and efficacy. It also describes major clinical consequences of immune responses to therapeutic protein products and offers recommendations for risk mitigation in the clinical phase of development.

Category	Title	Date	Significance
Biosimilarity	Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product	May 13, 2014	The draft guidance discusses some of the overarching concepts related to clinical pharmacology testing for biosimilar products, approaches for developing the appropriate clinical pharmacology database, and the utility of modeling and simulation for designing clinical trials.
Clinical Pharmacology	Drug Interaction Studies--Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations	February 17, 2012	The draft guidance represents a major update to an earlier guidance document on this topic. The updated draft includes new material that specifically addresses potential therapeutic protein-drug interactions.
Biosimilarity	Scientific Considerations in Demonstrating Biosimilarity to a Reference Product	February 9, 2012	The draft guidance gives an overview of FDA's approach to determining biosimilarity, consistent with a longstanding Agency approach to evaluation of scientific evidence. The guidance explains the FDAs intent to consider the totality of the evidence provided by a sponsor to support a demonstration of biosimilarity, and recommends that sponsors use a stepwise approach in their development of biosimilar products.
Biosimilarity	Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product	February 9, 2012	The draft guidance is intended to provide recommendations to applicants on the scientific and technical information of the chemistry, manufacturing, and controls (CMC) section of a marketing application for a proposed biosimilar product submitted under section 351(k) of the PHS Act. It describes the Agency's current thinking on factors to consider when demonstrating that a proposed protein product is highly similar to a reference product
Biosimilarity	Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009	February 9, 2012	This draft guidance provides answers to common questions from sponsors interested in developing proposed biosimilar products, biologics license application (BLA) holders, and other interested parties regarding FDA's interpretation of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). The Q&A format is intended to promote transparency and facilitate development programs for proposed biosimilar products by addressing questions that may arise in the early stages of development

IV. Advancing and Adopting Regulatory Science Relevant to Medical Devices

Under the Medical Devices Amendments Act of 1976, FDA is responsible for regulating firms who manufacture, repackage, relabel, and/or import medical devices sold in the United States. Medical devices are classified as Class I, II, or III, with regulatory control increasing from Class I to Class III. Most Class I devices are exempt from Premarket Notification 510(k); most Class II devices require Premarket Notification 510(k); and most Class III devices require Premarket Approval.

FDA is committed to fostering innovation in device development, assessment, and manufacturing, and to providing the public with accurate, science-based information about the devices it oversees. As technology advances, medical devices are becoming increasingly complex, and FDA must be able to anticipate these advances, creating the scientific tools that will assist industry in developing new products and assessing their safety, effectiveness, quality, and performance.

i. Progress in Advancing Regulatory Science Relevant to Medical Devices

The MDUFA Performance Goals for FY 2013-2017 do not contain specific commitments related to advancing regulatory science. However, because medical devices have been under regulatory review for over 30 years, FDA scientists have a longstanding engagement in research efforts to advance the science needed for their effective regulatory evaluation. Regulatory science activities include investigating how new devices interact with the body, developing test methods for new technologies, testing products to identify root causes of failure, and developing statistical and epidemiological methods to enhance both pre-market and post-market study designs.

A number of the examples presented below involve collaboration with international regulators, academic, and industry experts, often through working groups organized by scientific societies. As regulatory science progresses, medical device development and review will undergo refinement as knowledge gained from experience with pre- and post-market reviews is combined with scientific advances that support regulatory decision-making.

1. Recent accomplishments relevant to the development of safe and effective medical devices

Intramural Research Accomplishments in the Area of Medical Devices by Priority Area

Accomplishment	Significance
I Modernize Toxicology to Enhance Product Safety	
The safety of metal-oxide coatings on medical devices. CDRH researchers used a variety of cell-based toxicity assays to assess the safety of zinc oxide coatings, which because of their antimicrobial and UV-resistant properties have wide applications for coating medical devices. P. E. Petrochenko, Q. Zhang, M. R. Bayati, S. A. Skoog, K. Scott Phillips, G. Kumar*, et al.*, Cytotoxic Evaluation of Nanostructured Zinc Oxide (ZnO) Thin Films and Leachates,"*Toxicology in Vitro,* 2014.	Metal oxide coatings with nanometer-scale patterning have significant potential to improve performance of medical devices but may have adverse effects at the cellular level due to particulates and metal leaching at the implant site. The study found that zinc ions leaching from the films had toxic effects on mammalian cells, suggesting a need for careful testing of the safety of products with these coatings.
Learning how to determine the genotoxicity of nanomaterials. This study examined the physical state in different media of titanium oxide nanoparticles and their association with, and uptake by, bacteria commonly used to assess the mutagenicity of new compounds. A variety of tests of genotoxicity were performed. Although the nanoparticles readily associated with the bacteria, they were not internalized and did not increase mutation rates. K. S. Butler, B. J. Casey, G. V. M. Garborcauskas, B. J. Dair, and R. K. Elespuru, "Assessment of titanium dioxide nanoparticle effects in bacteria: Association, uptake, mutagenicity, co-mutagenicity and DNA repair inhibition," *Mutation Research/Genetic Toxicology and Environmental Mutagenesis,* vol. 768, pp. 14-22, 7/1/ 2014	The mutagenicity of chemical compounds intended for medical use is typically assessed using bacteria. Nanoparticles present special challenges for such assays, in part because they may not be readily taken up. This study will inform design of appropriate testing procedures to assess the genotoxicity of nanomaterials.
II Stimulate Innovation in Clinical Evaluations and Personalized Medicine to Improve Product Development and Patient Outcomes	
How to assess the performance of diagnostic procedures. The investigators re-examined observer performance studies used to evaluate mammographic imaging to detect breast cancer. They compared the results that were obtained for two alternative endpoints that can be derived from the receiver operating characteristic curves and used to summarize the diagnostic performance. The researchers found that the endpoints were highly concordant and led to similar inferences. C. K. Abbey, B. D. Gallas, J. M. Boone, L. T. Niklason, L. M. Hadjiiski, B. Sahiner, et al., Comparative Statistical Properties of Expected Utility and Area Under the ROC Curve for Laboratory Studies of Observer Performance in Screening Mammography," Academic radiology, vol. 21, pp. 481-490, 2014.	This work suggests that endpoints that are potentially more reflective of diagnostic utility may prove useful in evaluating diagnostic procedures.

Accomplishment	Significance
Pooling data to improve cardiac care of patients with heart disease. The investigators pooled clinical trial data submitted to the FDA and compared the benefits of cardiac resynchonization therapy in men and women and according to degree of heart failure. R. Zusterzeel, K. A. Selzman, W. E. Sanders, D. A. Caños, K. M. O'Callaghan, J. L. Carpenter*, et al.*, "Cardiac resynchronization therapy in women: US Food and Drug Administration meta-analysis of patient-level data," *JAMA internal medicine,* vol. 174, pp. 1340-1348, 2014.	The investigators merged multiple data sets from submissions to FDA to create sufficient statistical power for assessment of cardiac resynchronizaton therapies on woman. The results suggested that a class of female patients with heart failure who are not typically treated with this type of therapy would receive clinically significant benefit.
III Support New Approaches to Improve Product Manufacturing and Quality	
Ensuring the quality of intraocular lenses. FDA researchers assessed the impact of changing the beam diameter in confocal laser microscopy for the evaluation of the dioptric powers of intraocular lenses. Dioptic power is an important determinant of the efficacy of these devices, and its accurate assessment is a major factor in implanting the appropriate lens for improving vision. B. N. Walker, R. H. James, A. Chakravarty, D. Calogero, and I. K. Ilev, "Assessing the effect of laser beam width on quantitative evaluation of optical properties of intraocular lens implants," *Journal of biomedical optics,* vol. 19, p. 055004, 2014/05// 2014.	Confocal laser microscopy is a technique that can improve the resolution, accuracy, and repeatability of optical measurements. The results demonstrate its potential for more effective and quantitative evaluation of intraocular lenses.
Determining ultrasound exposure. CDRH investigators compared two analytic approaches for measuring the magnitude of ultrasound using hydrophones. The authors found that a method based on deconvolution of hydrophone sensitivity improved the accuracy and precision of measurements of ultrasound pressure and intensity. K. A. Wear, P. M. Gammell, S. Maruvada, Y. Liu, and G. R. Harris, "Improved measurement of acoustic output using complex deconvolution of hydrophone sensitivity," *Ultrasonics, Ferroelectrics and Frequency Control, IEEE Transactions on,* vol. 61, pp. 62-75, 2014.	The work will inform methods used to assess potentially harmful sonic exposures from a growing variety of instruments based on ultrasound that are becoming part of clinical practice.
Virtual humans to improve device safety. CDRH and its collaborators developed a computational "Virtual Family" of anatomically correct models, consisting of an adult male, an adult female, and two children. These models are now being used to investigate how various devices interact with the body. M.-C. Gosselin, E. Neufeld, H. Moser, E. Huber, S. Farcito, L. Gerber*, et al.*, "Development of a new generation of high-resolution anatomical models for medical device evaluation: the Virtual Population 3.0," *Physics in medicine and biology,* vol. 59, p. 5287, 2014.	These advanced computational models can help speed the design and testing of new and improved devices by allowing developers to test early versions of the device on the computer model instead of on people. This can minimize the risk to patients, speed development, and reduce costs.

Accomplishment	Significance
Understanding the biologic effects of neural implantation. CDRH researchers used an angiographic technique (speckle variance optical coherence angiography) to characterize the response of vascular tissue in live mice to surgical procedures associated with implantation of a neuroprosthetic device (for example, an implanted device that would allow a patient to control a prosthetic limb). D. X. Hammer, A. Lozzi, E. Abliz, N. Greenbaum, A. Agrawal, V. Krauthamer*, et al.*, "Longitudinal vascular dynamics following cranial window and electrode implantation measured with speckle variance optical coherence angiography," *Biomedical optics express,* vol. 5, pp. 2823-2836, 2014.	The high-resolution in vivo imaging of changes in cranial vascular permitted by this angiographic technique may prove useful to understanding the biological effects of neural implantation and aid in the development of novel neural prostheses.
Evaluating biosensors to help treat diabetes. CDRH researchers identified a set of performance test methods for biosensors that used Forster resonance energy transfer (FRET) to quantify glucose concentrations and then used these test methods to assess performance of FRET biosensors that they had fabricated. M. Aloraefy, T. J. Pfefer, J. C. Ramella-Roman, and K. E. Sapsford, "In vitro evaluation of fluorescence glucose biosensor response," *Sensors (Basel),* vol. 14, pp. 12127-48, 2014.	Glucose biosensors have the potential to permit continual *in vivo* monitoring of glucose levels in diabetic patients, improve patient compliance, and allow patients and physicians to achieve better control of glucose levels. This research was intended to facilitate evaluation of optical glucose biosensors throughout the development process and promote technological innovation, thus hastening realization of new clinical options for diabetics.
V Harness Diverse Data through Information Sciences to Improve Health Outcomes	
Simulation to understand how devices behave in the body. Harnessing molecular dynamics simulations to improve the safety and effectiveness of devices. CDRH researchers used molecular dynamics simulations to successfully predict diffusion in a complex polymeric coating used in stents. C. Forrey, D. M. Saylor, J. S. Silverstein, J. F. Douglas, E. M. Davis, and Y. A. Elabd, "Prediction and validation of diffusion coefficients in a model drug delivery system using microsecond atomistic molecular dynamics simulation and vapour sorption analysis," *Soft matter,* vol. 10, pp. 7480-7494, 2014.	Unintended leaching of molecules from materials in implanted devices creates a broad range of public health concerns, but this release is difficult to assess experimentally. The work demonstrated the usefulness of simulation approaches to predict diffusion that could potentially be applied to the evaluation of a large number of medical devices.
Evaluating biomarkers based on imaging techniques. FDA researchers and partners in the Radiological Society of North America Quantitative Imaging Biomarkers Alliance reviewed various study designs for comparing quantitative imaging biomarker (QIB) algorithms and proposed a series of steps for establishing the performance of these algorithms. N. A. Obuchowski, A. P. Reeves, E. P. Huang, X.-F. Wang, A. J. Buckler, H. J. G. Kim*, et al.*, "Quantitative imaging biomarkers: A review of statistical methods for computer algorithm comparisons," *Statistical methods in medical research,* p. 96,, 2014.	Complex algorithms are typically used to generate values for biomarkers based on various forms of medical imaging. This work provides guidance to regulators on assessing the statistical validity of these biomarkers and comparing alternative algorithms.

Accomplishment	Significance
VII Facilitate Development of Medical Countermeasures to Protect Against Threats to U.S. and Global Health and Security	
Development of a mobile app for medical device users. In collaboration with Boston Children's Hospital and Harvard Medical School, FDA researchers developed the Medwatcher mobile app for reporting medical device errors and malfunctions. Boston Children's Hospital, Harvard Medical School (Dec. 1, 2014) MedWatcher, https://medwatcher.org/	This new app provides a point-of-care interface for reporting adverse events related to medical devices. Importantly, it can collect data on the environment of use, and other factors affecting medical countermeasure medical devices to assess effective use during emergency events.

2. Public-private partnerships conducting research in the area of medical devices

Research Accomplishments by FDA's Public-Private Partnerships in the Area of Medical Devices

Public-Private Partnership	Participants	Mission	Recent (2013-2014) Accomplishments
Medical Device Innovation Consortium (MDIC)	Medical device industry, Patient organizations, non-profit groups, and Federal agencies (NIH and CMS)	MDIC aims to advance regulatory science in the medical device industry. MDIC will coordinate the development of methods, tools, and resources used in managing the total product life cycle of a medical device to improve patient access to cutting-edge medical technology.	• Project launched on clinical trial innovations that will simplify trials and accelerate access to breakthrough technologies. Efforts from stakeholders have focused on determining what can be done to bring first-in-human trials to the US. MDIC is also looking into how data can be handled more effectively—what kind of data is needed for collection, how it is organized and stored, and when it can be shared across studies. • MDIC is developing a framework for incorporating patient preferences into the device assessment process. MDIC plans to publish a methods framework and catalogue on how patient preference information can be collected and used to develop, design, and market devices that meet patient needs. • MDIC is working to expand the use of regulatory grade computer models & simulations to increase confidence in device safety and efficacy and advance device development. Efforts include strategies to verify and validate computational models so that they can be used to reduce pre-clinical and clinical testing of devices and speed innovation. Seven working groups have been established in this area. • MDIC has launched a project on "Case for Quality" to create a forum and research what factors are critical to device quality.

Public-Private Partnership	Participants	Mission	Recent (2013-2014) Accomplishments
Medical Device Epidemiology Network (MDEpiNet)	Patients and patient organizations, academic researchers, medical device industry, international regulators and researchers, hospital representatives, health insurance providers, contract research organizations, other HHS components (CMS, AHRQ, ONC, NIH)	To develop national and international infrastructure and innovative methodological approaches to conduct robust studies and surveillance to advance our understanding of safety and effectiveness of medical devices throughout their life cycle through public private partnership with academia and other stakeholders	• Launched international consortia of registries of orthopedic implants, transcatheter aortic valves, and vascular graft devices to promote global surveillance of critical medical devices. • Launched a registry task force, charged with: Identifying existing registries that may contribute to a National Medical Device Post-market Surveillance System; Leveraging registry efforts on quality improvement, reimbursement, patient centered outcomes; Identifying priority medical device types for which the establishment of a longitudinal registry is important; Identifying and prioritizing successful registry governance and data quality best practices, and; Developing strategies for the use of registries to support premarket approval and clearance as well as post-market indication extensions in labeling. • Installed the Data Extraction and Longitudinal Trend Analysis (DELTA) system software on National Cardiovascular Data Registries to begin prospective active surveillance of medical devices.

ii. Progress in Adopting Regulatory Science Relevant to Medical Devices

1. Scientific training offered by CDRH in FY 2014

Recent Scientific Courses in CDRH

Course	Description
AAMI Industrial Sterilization for Medical Devices	This was a comprehensive 4-day course covering essential information on sterilization technologies and methods, sterilization standards, FDA requirements, critical factors in product design, and product release decisions.
Basics of Flow Cytometry	This course provided an introduction to flow cytometry, a powerful technique in many fields, including diagnosis of hematological malignancy, detection of minimal residual disease (MRD), determination of CD4/CD8 ratio in HIV, and nanotechnology.
Basics of Human Factors Engineering and Device Design	Human factors engineering is a discipline that blends engineering design with human psychology, kinesiology, and biomechanics. The goal of the course was to apply knowledge of human cognition and physical limitations to the design of systems, such as tools, tasks, devices, software, and work areas.
Regenerative Medicine Series	The Regenerative Medicine Seminar Series offered a variety of thought-provoking seminars that examined restoration and function of the human form within the context of translational research involving medical devices and biologics.
CDRH Science Sharing Seminar	This seminar series consisted of bi-weekly one-hour presentations by CDRH staff on a wide variety of scientific topics related to medical devices.
Statistics for Diagnostic Devices	This course on applied statistics for medical devices consisted of eight sessions in 2014.

2. Public workshops to advance the development of medical devices

Progress in educating and getting input from the stakeholder community is accomplished in a number of venues. FDA personnel give numerous presentations at scientific meetings and academic seminars. In addition to providing extensive materials on its website, the FDA sponsors workshops, public meetings, and webinars. For devices, illustrative examples are listed in the table below.

Recent Workshops Focusing on Medical Device Development

Activity	Date	Purpose
Additive Manufacturing of Medical Devices: An Interactive Discussion on the Technical Considerations of 3D Printing	October 8-9, 2014	The purpose of this workshop was to provide a forum for FDA, medical device manufactures, additive manufacturing companies, and academia to discuss technical challenges and solutions of 3D printing. The Agency would like input regarding technical assessments that should be considered for additively manufactured devices to provide a transparent evaluation process for future submissions.
International Medical Device Regulators Forum (IMDRF)	September 15-19, 2014	The purpose of this meeting was to bring together medical device regulators from across the world to share best practices and harmonize medical device regulation worldwide.
Revamping Microbiological Test Methods for Contact Lenses, Products and Accessories to Protect Health and Ensure Safety	September 12, 2014	The purpose of this workshop was to discuss adequate testing of contact lens care products for disinfection efficacy against emerging pathogens as well as common infectious etiologies.
Proteomics in the Clinic	June 13, 2014	The topic discussed was the state of the art and challenges surrounding validation of proteomic methodologies for in vitro diagnostic tests.
Proposed Risk-Based Regulatory Framework and Strategy for Health Information Technology	May 13-15, 2014	The FDA, ONC, and FCC sought broad input from stakeholders and experts. The topic discussed was the FDASIA health IT report that contained a proposed strategy and recommendations on an appropriate, risk-based regulatory framework for health IT that promotes innovation, protects patient safety, and avoids regulatory duplication.
Methods for Thrombogenicity Testing	April 14, 2014	The purpose of this workshop was to discuss the advantages and limitations of both in vivo and in vitro thrombogenicity test methods.
Advancing Regulatory Science for High Throughput Sequencing Devices for Microbial Identification and Detection of Antimicrobial Resistance Markers	April 1, 2014	The purpose of this workshop was to discuss the clinical and public health applications and performance validation of these high throughput sequencing devices, the quality criteria for establishing the accuracy of reference databases for regulatory use and ways to streamline clinical trials for microbial identification.
FDA/AAO Workshop on Developing Novel Endpoints for Premium Intraocular Lenses	March 28, 2014	The purpose of this workshop was to discuss current challenges in the assessment of innovative intraocular lens (IOL) designs with a focus on endpoint methodologies used in evaluating IOL safety and effectiveness.

Activity	Date	Purpose
Regulatory Science and Sustainable Implementation of National and International Medical Device Registries	March 24, 2014	This program focused on highlighting the regulatory infrastructure and principles that will leverage medical device registries linked with relevant data sources, and harmonized methodological principles (including surveillance, targeted studies, research, and potential application to support premarket applications).
International Consortium of Orthopedic Registries meeting at American Academy of Orthopedic Surgeons	March 10-11, 2014	Presented total joint arthroplasty findings from 8 international ICOR studies, Discussed future international registry collaborations and FDA's pre/post market device assessment strategy.
Summit on Healthcare Technology in Non Clinical Settings	October 9-10, 2013	The event brought together leaders from the medical device industry and regulatory bodies, clinicians from healthcare institutions, researchers, and others to identify, discuss, and formulate strategic initiatives and priorities focused on ensuring the safety and effectiveness of medical technology in nonclinical settings.
The Patient Preference Initiative: Incorporating Patient Preference Information into the Medical Device Regulatory Process	September 18-19, 2013	This workshop brought together industry, patient advocates, and other interested parties to discuss how to incorporate patient views and preferences across the total device product lifecycle.
Battery-Powered Medical Devices Workshop: Challenges and Opportunities	July 30-31, 2013	The FDA organized a Battery-Powered Medical Devices Workshop on July 30-31, 2013 to create awareness of the potential challenges related to battery-powered medical devices and to collaboratively develop ways of ensuring the continued performance and reliability of these devices.
510(k) Device Modifications: Deciding When to Submit a 510(k) for a Change to an Existing Device	June 13, 2013	The purpose of the meeting was to discuss FDA's past, present, and future policy on 510(k) Modifications with external stakeholders. FDA seeks comment from stakeholders on different options, both in the form of submissions to the docket for the Federal Register notice associated with this meeting and in discussion during the public meeting.
FDA/NIH/NSF Workshop on Computer Models and Validation for Medical Devices	June 11-12, 2013	The purpose of the meeting was to present, discuss and receive input on an FDA library of models and data relevant to medical devices and to discuss a strategy to assess the credibility of computer models used to evaluate medical devices.
Summit on Color in Medical Imaging	May 8-9, 2013	The purpose of the workshop was to bring together key stakeholders to clearly identify areas of need, investigate solutions and propose best-practice approaches. The recommendations of the summit might include the creation of a technical special interest group either as part of the ICC or in some other forum and the establishment of best-practice guidelines for industry.
Home Use of Diabetes and Cardiovascular Medical Devices	April 23, 2013	The speakers discussed the FDA's efforts to support the safe and effective use of medical devices in the home, including new technology that is focused on self-care and self-monitoring in the area of diabetes and cardiovascular disease.
Clinical Flow Cytometry in Hematologic Malignancies	February 25-26, 2013	The purpose of this public workshop was to seek input from academia, Government, laboratorians, industry, clinicians, patients and other stakeholders on the role of clinical flow cytometry in hematologic malignancies, in order to develop a specific regulatory policy for this class of in vitro diagnostic devices.

3. Guidance development to enhance medical device development

One of the important outcomes of advancing regulatory science is its incorporation into guidance that can provide sponsors with recommendations intended to bring predictability to the medical device development and review process. The table below includes examples of guidances that further the goals of MDUFA.

Recent Guidances to Foster Development of Medical Devices

Title	Date
Evaluation of Sex-Specific Data in Medical Device Clinical Studies; Guidance for Industry and Food and Drug Administration Staff	August 22, 2014
In Vitro Companion Diagnostic Devices; Guidance for Industry and FDA Staff	August 6, 2014
Design Considerations for Devices Intended for Home Use; Guidance for Industry and Food and Drug Administration Staff	August 5, 2014
Benefit-Risk Factors To Consider When Determining Substantial Equivalence in Premarket Notifications [510(k)] With Different Technological Characteristics; Draft Guidance for Industry and Food and Drug Administration Staff	July 15, 2014
Guidance for Industry: Considering Whether a Food and Drug Administration-Regulated Product Involves the Application of Nanotechnology	June 27, 2014
Global Unique Device Identification Database; Guidance for Industry and Food and Drug Administration Staff	June 27, 2014
Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communication Devices; Draft Guidance for Industry and Food and Drug Administration Staff	June 25, 2014
Draft Guidance for Industry on Internet/Social Media Platforms With Character Space Limitations: Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices	June 18, 2014
Surveying, Leveling, or Alignment Laser Products; Draft Guidance for Industry and Food and Drug Administration Staff	May 5, 2014
Live Case Presentations During Investigational Device Exemption Clinical Trials; Draft Guidance for Institutional Review Boards, Industry, Investigators, and Food and Drug Administration Staff	April 17, 2014
Endotoxin Testing Recommendations for Single-Use Intraocular Ophthalmic Devices; Draft Guidance for Industry and Food and Drug Administration Staff	April 17, 2014
Medical Devices Containing Materials Derived From Animal Sources (Except for In Vitro Diagnostic Devices); Draft Guidance for Industry and Food and Drug Administration Staff	January 23, 2014
Reporting of Computational Modeling Studies in Medical Device Submissions; Draft Guidance for Industry and Food and Drug Administration Staff	January 17, 2014

Title	Date
Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use; Draft Guidance for Industry and Food and Drug Administration Staff	January 7, 2014
Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use; Draft Guidance for Industry and Food and Drug Administration Staff	January 7, 2014
Medical Device Development Tools; Draft Guidance for Industry, Tool Developers, and Food and Drug Administration Staff	November 14, 2013
Design Considerations for Pivotal Clinical Investigations for Medical Devices; Guidance for Industry, Clinical Investigators, Institutional Review Boards and Food and Drug Administration Staff	November 7, 2013
Mobile Medical Applications; Guidance for Industry and Food and Drug Administration Staff	September 25, 2013
The Applicability of Good Laboratory Practice in Premarket Device Submissions: Questions and Answers; Draft Guidance for Industry and Food and Drug Administration Staff	August 28, 2013
Implanted Blood Access Devices for Hemodialysis; Draft Guidance for Industry and Food and Drug Administration Staff	June 28, 2013
Guidance for Industry on Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality	June 25, 2013
Content of Premarket Submissions for Management of Cybersecurity in Medical Devices; Draft Guidance for Industry and Food and Drug Administration Staff	June 14, 2013
Assay Migration Studies for In Vitro Diagnostic Devices; Guidance for Industry and Food and Drug Administration Staff	April 25, 2013
Molecular Diagnostic Instruments With Combined Functions; Draft Guidance for Industry and Food and Drug Administration Staff	April 9, 2013
Guidance for Industry and Food and Drug Administration Staff: Investigational Device Exemption Guidance for Retinal Prostheses	March 6, 2013
Pulse Oximeters-Premarket Notification Submissions [510(k)s]; Guidance for Industry and Food and Drug Administration Staff	March 4, 2013
Draft Guidance for Industry and Food and Drug Administration Staff; Design Considerations for Devices Intended for Home Use	December 13, 2012
Guidance for Industry and Food and Drug Administration Staff; The Content of Investigational Device Exemption and Premarket Approval Applications for Artificial Pancreas Device Systems	November 23, 2012
Draft Guidance for Industry and Food and Drug Administration Staff; Highly Multiplexed Microbiological/Medical Countermeasure In Vitro Nucleic Acid Based Diagnostic Devices	November 9, 2012

V. Compilation of FDA's Regulatory Science Activities (FY 2013-2014)

In this section of this report we provide summary information on Intramural regulatory science research programs at FDA based on metrics provided in the *Strategy and Implementation Plan for Advancing Regulatory Science for Medical Products.*

i. Addressing Scientific Gaps

1. Scientific publications

Scientific Publications* by Type and Center

Category‡	CBER FY13/FY14	CDER FY13/FY14	CDRH FY13/FY14	Joint FY13/FY14	Totals FY13/FY14
Article	187/196	250/294	97/153	51/60	585/709
Editorial	8/6	36/24	8/11	6/6	58/47
Letter	10/10	14/18	4/0	1/2	29/30
Review	7/2	26/29	3/8	4/3	44/49
Regulatory Summary	6/14	5/10	2/1	0/2	7/12

* Publication statistics are from the FDA publications database.
‡ Not included are 16 book chapters authored by FDA staff.

2. Cross-cutting competitive funding programs

To maximize its investment in intramural regulatory science programs, FDA and its medical product Centers manage a number of competitive intramural funding programs that offer review and laboratory scientists competitive opportunities to address defined priorities which align with the program's public health emphasis. These programs are not targeted to specific user fee program goals, but focus on general priority areas of regulatory science or public health (note: the Regulatory Science Program described under GDUFA, which provides funding for regulatory science projects related to the GDUFA program, is covered specifically in the GDUFA section of this report). Among the programs that make competitive awards based on identified regulatory science needs are the following:

CDER Intramural Funding Programs: The "Regulatory Science and Review Enhancement" (RSR) Program supports FDA scientific staff in the CDER by offering competitive opportunities to explore approaches, methods, or data that could potentially enhance the quality or efficiency of CDER's application review process, or the design and evaluation of clinical or non-clinical protocols and safety evaluation. Extant since the mid-1990's, provides small 1-year grants that enable scientist to support part time project help or conduct a small pilot project.

- The RSR program made 15 awards in 2013 and 12 awards in 2014. Projects are addressing a range of regulatory science questions, including statistical approaches to clinical trials, bioequivalence studies, and biosimilarity assessments; sterile filtration processes; control of biologics manufacture, and methods related to product quality and design.

- The CDER Critical Path funding program, is designed to stimulate and facilitate the modernization of the sciences through which FDA-regulated products are developed, evaluated, and manufactured by (1) evaluating and standardizing existing and new technologies used in the discovery, development and production of regulated products (2) Identifying and developing solutions to new concerns likely to arise regarding the safety, quality and efficacy of these products, and (3) providing the scientific basis on which to base new policies, regulations and procedures. Critical Path awards were made to 19 and 11 CDER researchers in 2013 and 2014, respectively.

CBER Intramural Funding Programs: CBER's Intramural Funding Program is an open, competitive, peer-reviewed grant program. It supports the advancement of regulatory science and helps to address center and office-specific research priorities and gaps of current and anticipated products in three general areas, product safety, product efficacy, and product characterization. Proposals are submitted every other year; progress reports are required for a second year of funding. In addition to peer-review, proposals are reviewed by management to ensure that projects are relevant to priorities, have feasible outcomes, and are high quality research. Proposals are funded from three programs: Critical Path, Modernizing Science and Pandemic Flu.

- 52 CBER Intramural projects were funded in FY 2013.
- 79 CBER Intramural projects were funded in FY 2014.

FDA Office of the Chief Scientist Intramural Funding Programs: Office of the Chief Scientist provides Challenge Grants in specific priority areas to fund work not otherwise supported by FDA programs, including collaborations across organization boundaries. The funded projects address regulatory science topics pertinent to all parts of the agency. In FY 2014, the FDA Office of the Chief Scientist integrated 5 Challenge Grant intramural funding programs into a single submission and review process. In FY 2014, 230 concept proposals were submitted for these five grant categories. Of these, 41 were selected through competitive reviews to receive funding for FY 2014.

- Medical Countermeasures Initiative Challenge Grants; 13 proposals were funded in FY 2014. The projects are addressing topics that include product quality, potency and delivery systems for medical countermeasures, and methods development for detection or diagnostics.

- Nanotechnology Challenge Grants - Collaborative Opportunities for Research Excellence in Science (CORES) Program; 6 proposals were funded in FY 2014. The ongoing projects are addressing the biological effects and characterization on nanomaterials.

- Chief Scientist's Challenge Grants; 7 proposals were funded in FY 2014. The ongoing projects are addressing topics ranging from antibiotic resistance and pathogen detection to medical product safety and product quality.

- Office of Minority Health Challenge Grants; 2 projects were funded in FY 2014. Projects focus is on understanding biomarkers in minority populations.

- Office of Women's Health Challenge Grants; 13 proposals were funded in FY 2014. The ongoing projects are addressing refinement of imaging techniques.

3. Scientific collaborations to advance regulatory science

2. Scientific Exchange and Collaborations to Advance Regulatory Science
Metric: For each of the categories of activity listed below, provide a description of activities within that category. Where available, include quantitative summaries of activities and information on participating organizations, purpose, and outcomes for that activity.
- participation in public private partnerships and consortia and external regulatory science collaborations
- workshops
- interactions with sister public health agencies (e.g.., joint working groups).

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FDA's Public-private partnerships (consortia) enable collaborative efforts between FDA, industry and academia, managed by non-profit neutral third parties. These partnerships permit the efficient leveraging of scientific resources and enlist needed expertise across the drug development community to foster medical product development. Of note, many of these consortia are focused on the development of tools to aid in the development of medical products, including biomarkers, clinical outcome assessments, data standards and clinical trial designs.

FDA's Public-Private Partnerships Devoted to Medical Product Development and Their Recent Accomplishments

Consortia	Partners	Mission	Key Recent Accomplishments
The Analgesic Clinical Trial Translations, Innovations, Opportunities and Networks Initiative (ACTTION)[25]	International and domestic industry and professional societies	Streamline discovery and development process for new analgesic drug products Address gaps in scientific information which can slow down analgesic clinical trials and analgesic drug development	Completed a comprehensive CDISC (Clinical Data Interchange Standards Consortium) compliant pain standard for analgesic clinical trials in collaboration with CDISC. This standard was accepted by the FDA in the NDA and IND submissions. Published 11 peer-reviewed papers in the area of analgesics, anesthetics and addiction treatment drugs.
Biomarkers Consortium (BC)[26]	Stakeholders across the health enterprise, including government, industry, academia, patient advocacy, and other non-profit private sector organizations	To discover, develop, and qualify biological markers (biomarkers) to support new drug development, preventive medicine, and medical diagnostics.	Established a standardized carotid MRI protocol and determined the impact of site/platform on reproducibility of the measurements Developed improved, more sensitive radioligands with higher binding to the peripheral benzodiazepine receptor Disease areas of biomarker research conducted by consortium members included Sarcopenia (6 publications), Osteoarthritis (1), Bacterial Infections (1), and cancer (1), and neuroinflammation (1).
The Coalition Against Major Disease (CAMD) Consortium[27]	Scientists from pharmaceutical and biotechnology companies, patient advocacy organizations, academic advisors, and representatives from regulatory agencies	Develop new tools (biomarkers and disease progression models) and methods that can be applied during the development of new treatments for neurodegenerative diseases.	Developed quantitative simulation tool that models the progression of Alzheimer's Disease and will help investigators make informed decisions about design of clinical trials of treatment for this disease.

[25] www.acttion.org
[26] www.biomarkersconsortium.org/about.php
[27] www.c-path.org/CAMD.cfm

Consortia	Partners	Mission	Key Recent Accomplishments
The Clinical Trials Transformation Initiative (CTTI)[28]	CMS; NIH; pharmaceutical, biotech, device and clinical research organizations; patient advocacy groups, professional societies and academic institutions	Identify practices that through broad adoption will increase the quality and efficiency of clinical trials.	Conducted a survey of sponsors and a workshop to better understand the barriers that sponsors perceived to following the adverse event reporting rule issued by FDA. Issued recommendations for improving processes and procedures around safety reporting Produced a white paper that outlines strategies for using the Mini-Sentinel distributed database to conduct clinical trials
The Critical Path to TB Drug Regimens (CPTR) Consortium[29]	Bill & Melinda Gates Foundation, Reagan-Udall Foundation, the Global Alliance for TB Drug Development, and the Critical Path Institute	Accelerate the development of new TB regimens by catalyzing innovative testing methods, product development partnerships and novel development strategies to develop innovative tools that will significantly accelerate development of new TB medicines.	Created a database of clinical trials of TB regimens Initiated six modeling and simulations studies on TB in defined patient populations Submitted a dossier to the EMA on the Hollow Fiber system model for TB for consideration as a drug development tool
Cardiac Safety Research Consortium (CSRC)[30]	Stakeholders from industry, academia, and government	Advance scientific knowledge on cardiac safety for new and existing medical products by building a collaborative environment based upon the FDA's Critical Path Initiative and other public health priorities	Initiated clinical study in healthy subjects to determine if the dedicated thorough QT study can be replaced by analysis of ECG data generated from First-in-Man single ascending dose studies Published numerous reports on cardiovascular safety in the context of drug development Numerous think tanks and workshops (a complete list is available at https://www.cardiac-safety.org/think-tanks)
The Polycystic Kidney Disease Outcomes (PKDOC) Consortium[31]	Scientists from pharmaceutical and biotechnology companies, patient advocacy organizations, academic advisors and representatives from FDA, EMA, and NIH	Develop CDISC data standards for PKD and use clinical data from autosomal-dominant PKD patients in patient registries and observational studies to support the FDA and EMA qualification of an imaging biomarker (Total Kidney Volume) for use in drug development trials	Submitted briefing package to FDA and EMA for prognostic biomarker (total kidney volume) for use in clinical trial enrollment Launched polycystic Kidney Disease User Guide, a clinical data standard that provides guidance on standardization of PKD data in regulatory submissions (e.g., new drug applications)

[28] http://www.ctti-clinicaltrials.org/
[29] www.c-path.org/CPTR.cfm
[30] www.cardiac-safety.org
[31] www.c-path.org/PKD.cfm

Consortia	Partners	Mission	Key Recent Accomplishments
The Patient Reported Outcome (PRO) Consortium[32]	Scientists from pharmaceutical and biotechnology companies, patient advocacy organizations, academic advisors, and representatives from (FDA, EMA), and NIH	Develop, evaluate, and qualify PRO instruments with the FDA for use in clinical trials designed to evaluate the safety and effectiveness of medical products	Developed draft PRO instruments, using patient input, for Depression, Cognition (mild cognitive impairment), Irritable Bowel Syndrome, Asthma, and Non-Small Cell Lung Cancer. The Cognition Working Group's draft instrument has been incorporated into a prevention trial of anti-amyloid treatment among individuals positive for amyloid but without an Alzheimer's disease (AD) diagnosis) Workshop, entitled, "Honoring the Past, Navigating the Present, Charting the Future"
The Predictive Safety Testing Consortium (PSTC)[33]	FDA, EMA and PMDA, and representatives of the pharmaceutical industry	Qualify new biomarkers for the detection and monitoring of drug-induced toxicity in preclinical and clinical studies	Developed data supporting two biomarkers of nephrotoxicity, submitted this data to regulatory agencies, and received Letter of Support from FDA The Vascular Injury working group published recommendations for sample collection and processing, analytical methods, and confirmation of target localization for development of biomarkers for drug-inducedvascular injury
International Serious Adverse Events Consortium (iSAEC)[34]	Representatives of the pharmaceutical industry, the Wellcome Trust, regulatory authorities, and academic centers	Identify DNA-variants useful in understanding the risk of drug-related serious adverse events	Published the iSAEC data sharing model Completed genome-wide association study of susceptibility to drug-induced pancreatitis

[32] www.c-path.org/PRO.cfm
[33] www.c-path.org/pstc.cfm
[34] www.saeconsortium.org

Consortia	Partners	Mission	Key Recent Accomplishments
SmartTots[35]	The International Anesthesia Research Society, regulatory agencies, professional societies, academic research institutions, patient advocacy groups, industry and other government and nonprofit organizations	Address major gaps in scientific information concerning the safety of anesthetics and sedatives in pediatric age groups, focusing on the safety of inhaled and intravenous drugs in pediatrics	Awarded research grants to advance our understanding of the potential impact of anesthetics in the developing brains in animal models. (publications available at the SmartTots website) Established the SmartTots Speakers Bureau to provide representatives to speak about the safe use of anesthesia in children
Medical Device Innovation Consortium[36]	Medical device industry, Patient organizations, non-profit groups, and federal agencies (NIH and CMS)	MDIC aims to advance regulatory science in the medical device industry. MDIC will coordinate the development of methods, tools, and resources used in managing the total product life cycle of a medical device to improve patient access to cutting-edge medical technology.	Launched project on clinical trial innovations that will simplify trials and accelerate access to breakthrough technologies. Efforts from stakeholders have focused on determining what can be done to remove obstacles to bring first-in-human trials to the US. MDIC is also looking into how data can be handled more effectively—what kind of data is needed for collection, how it is organized and stored, and when it can be shared across studies. Launched a project on Case for Quality to create a forum and research what factors are critical to device quality

[35] www.smarttots.org
[36] www.asn-online.org/khi/mission.aspx

Consortia	Partners	Mission	Key Recent Accomplishments
HESI Cardiac Safety Technical Committee[37]	Academia, FDA and industry	Improve prediction of drug-induced cardiac safety issues	Completed a proof-of-concept study to investigate new technologies for detection of incipient procoagulant and prothrombotic states and identified rodent models suitable for evaluation of novel biomarkers of hemostasis Conducted a series of multi-site experimental studies to evaluate the sensitivity and reproducibility of canine and rodent cardiac contractility assays Continued to support the Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative, which is intended to replace the thorough QT study. Projects were initiated by CDER to develop and validate in silico models of the human ventricular myocyte, identify and calibrate risk metrics, and inform standardization of patch clamp protocols for generating ion channel pharmacology data.
National Institute for Pharmaceutical Technology and Education (NIPTE)[38]	Academia, FDA, the NIH, and the pharmaceutical industry	Improve human health through a multi-university collaboration on leading scientific research to advance the quality, safety, affordability, and speed to market of medicines through interdisciplinary research and education in pharmaceutical technology	Three training programs ("Quality by Design of freeze drying proteins", "Biopharmaceutical Education" modules and "Continuous Manufacturing) to provide education for reviewers Nine peer-reviewed publications accepted or published to advance the understanding of 1) pharmaceutical manufacturing (focusing on crystallization, precipitation, drying, granulation and wet granulation) and 2) product characterization, including understanding of cocrystals, polymorphs and methodology for microbial and subvisible particle detection
Multiple Sclerosis Outcome Assessments Consortium (MSOAC)[39]	Industry, academia, government, patient representatives, and the National MS Society	Develop standards for assessing outcomes in clinical trials of MS therapies Collect, standardize, and analyze data about MS with the goal of qualifying a new clinician-reported outcome measure of disability as a primary endpoint for future MS trials	Led development of new clinical data standard for multiple sclerosis allowing clinical research data from various MS trials to be grouped for reporting, analysis and regulatory submissions

[37] www.hesiglobal.org/i4a/pages/index.cfm?pageid=3431
[38] www.nipte.org/
[39] www.c-path.org/MSOAC.cfm

Consortia	Partners	Mission	Key Recent Accomplishments
Coalition For Accelerating Standards and Therapies (CFAST)[40]	CDISC (Clinical Data Interchange Standards Consortium) and Critical Path Institute	Accelerate clinical research and medical product development by facilitating the creation and maintenance of data standards, tools and methods for conducting research in therapeutic areas important to public health	Launched Asthma Therapeutic Area (TA) User Guide to assist investigators in representing their data in regulatory submissions consistent with CDISC standards
Innovation in Medical Evidence Development and Surveillance (IMEDS) program[41]	Reagan-Udall Foundation, industry, academia, consumer groups, and regulatory and other government agencies	Advance science and tools to support post-market evidence generation on regulated products, including safety surveillance and evaluations, and facilitate utilization of a robust electronic healthcare data platform for generating better evidence on regulated products in the post-market settings	IMEDS research projects began in 2014 (a complete research agenda is available)[42]
Product Quality Research Institute[43]	Academia, industry, and FDA	Generate and share timely, relevant, and impactful information that advances drug product quality and development	Convened workshop on nanomaterials in pharmaceutical products and issued summary report Completed characterization for five materials of construction representative of packaging systems used for parenteral and ophthalmic drug products

[40] www.c-path.org/CFAST.cfm
[41] www.reaganudall.org/our-work/safety-and-better-evidence/imeds-program
[42] http://www.reaganudall.org/our-work/safety-and-better-evidence/imeds-program/
[43] www.pqri.org/index.asp

Consortia	Partners	Mission	Key Recent Accomplishments
Institute for Safe Medication Practices[44]	Healthcare practitioners, legislative and regulatory bodies, healthcare institutions, consumers, healthcare professional organizations, regulatory and accrediting agencies, employer and insurer groups, and the pharmaceutical industry	Advance patient safety worldwide by empowering the healthcare community, including consumers, to prevent medication errors	Published electronic biweekly newsletter (ISMP Medication Safety Alert) by e-mail that provides vital and potentially life-saving information about medication and device errors and adverse drug reactions to directors of pharmacy, nurses, physicians, and other key personnel Issued 2014 update on the Joint-commission medication-related standards, a webinar intended for hospital and health systems leadership, physicians, safety officers, and other medical staff
MicroArray Quality Control-III (MAQC-III)[45]	Major providers of microarray platforms and RNA samples, NIH, Environmental Protection Agency (EPA), National Institute of Standards and Technology (NIST), academic laboratories, and other stakeholders	Assess the technical performance of next-generation sequencing platforms by generating benchmark datasets with reference samples and evaluating advantages and limitations of various bioinformatics strategies for RNA and DNA analyses	Comprehensively assessed RNA sequencing performance for junction discovery and differential expression profiling and compared it to microarray and quantitative PCR data using complementary metrics Provided cumulative sequencing data sets with >100 billion reads as a public resource for testing future developments of RNA-seq, as required in clinical and regulatory settings

[44] www.ismp.org/default.asp
[45] www.fda.gov/ScienceResearch/BioinformaticsTools/MicroarrayQualityControlProject/

Consortia	Partners	Mission	Key Recent Accomplishments
Kidney Health Initiative (KHI)	Patient organizations, health professional organizations, research institutions, foundations, pharmaceutical, biotechnology and device manufacturers, dialysis providers, and US and international government agencies	Advance scientific understanding of the kidney health and patient safety implications of new and existing medical products, and foster the development of therapies for diseases that affect the kidney	Created a database, representing almost 1,000 lupus nephritis patients, that is being analyzed to identify a core set of outcome measures, biomarkers, surrogate markers, and clearly defined terms that should be incorporated into all lupus nephritis trials. Organized a workgroup comprised of FDA staff, academic nephrologists and pharmacologists, and representatives from the pharmaceutical and dialysis industries to address the paucity of data for guiding drug dosing of life-saving drugs given in the context of critical illness and acute kidney injury requiring continuous renal replacement therapy.
Observational Medical Outcomes Partnership	Foundation for the NIH, industry, academia, and other federal agencies and non-profit organizations.	Develop the scientific methodology needed for conducting active drug safety surveillance in observational databases.	Evaluated the performance of various analytical methods on their ability to identify true associations and avoid false findings, 2) developed tools and capabilities for transforming, characterizing, and analyzing disparate data sources across the health care delivery spectrum, and 3) established a shared resource so that the broader research community can collaboratively advance the science. Results of OMOP's research has been widely published and presented at scientific conferences, e.g., the annual OMOP Symposium. The OMOP Research Lab, a central computing resource developed to facilitate methodological research, was transitioned to the Reagan-Udall Foundation for the FDA under the Innovation in Medical Evidence Development and Surveillance (IMEDS) Program, and re-branded as the IMEDS Lab.

FDA's Centers of Excellence in Regulatory Science and Innovation (CERSI) are critical to Agency efforts to promote faster and better scientific approaches to advancing regulatory science. CERSI at the University of Maryland and Georgetown University are working closely with FDA on projects ensuring product safety, FDA's readiness for emerging technologies, and harnessing diverse data to improve public health. Through workshops and lectures, these Centers support extensive training in regulatory science— in the last two years the University of Maryland CERSI (M-CERSI) held 16 workshops and offered regulatory science lectures at which total attendance totaled over 1,800. M-CERSI has recently instituted a Master of Science in Regulatory Science, while its counterpart at Georgetown offers a unique concentration in regulatory science as part of the Master of Science in Clinical and Translational Research, as well as a two-year fellowship in regulatory science. The two Centers are also creating opportunities for visiting scientists from FDA and offering continuing education for Agency personnel.

Recent Research Accomplishments of CERSI at The University of Maryland and Georgetown

Research Project	Accomplishment	Significance
University of Maryland Center for Excellence in Regulatory Science Innovation		
Role of transporters in drug-drug interactions	Established a strong correlation between drug inhibitory potency on transporters (e.g., OCT2, MATE1, and MATE2-K) *in vitro* and pharmacokinetic changes *in vivo*. Li Q, Yang H, Peng X, Guo D, Dong Z, Polli JE, Shu Y. Ischemia/Reperfusion-Inducible Protein Modulates the Function of Organic Cation Transporter 1 and Multidrug and Toxin Extrusion 1. 2013 Jun 3. [Epub ahead of print] PMID: 23651427)	The research indicated that the inhibitory potency of a compound or drug on these transporters should be assessed in drug development and clinical patient care.
Evaluation of Patient-Prescriber Agreements Project	Conducted a series of focus groups to explore patient and prescriber perceptions of patient-prescriber agreements (PPAs) and identified areas on which future research to improve PPAs can focus—for example, recommendations for use, patient centered design of PPAs, and burden of compliance on patients and prescribers	This study provides new information on utilization and perceptions of PPAs that can help guide future research. In particular, understanding what content is important to patients will facilitate the development of a more patient-centered PPA.
Developing standards for imaging modalities	Evaluated the potential of 3-D printing as a platform for fabrication of tissue phantoms (phantoms are specially designed objects used to evaluate, analyze, and tune the performance of various imaging devices) 3D printing may provide a suitable platform for performance testing in bioimaging techniques that are based on photon detection.	The results suggested that 3D printing may provide a suitable platform for performance testing in bioimaging techniques that are based on photon detection.
Antipsychotic drug use in nursing home elders with dementia: longitudinal analysis of rates of use, rates of discontinuation, and the associated facility-level factors	This study characterized patterns of antipsychotic use and determined the prevalence of antipsychotic discontinuation among older long-stay nursing home residents.	This analysis of a nationally representative sample of elderly long-stay nursing home residents suggested most are continuous antipsychotic users. The discovered patterns of use provide a baseline for evaluating implementation of the antipsychotic reduction initiative of the Center for Medicare and Medicaid Services.

Research Project	Accomplishment	Significance
Georgetown CERSI		
Approaches and Costs for Sharing Clinical Research Data	Identified and examined approaches and cost considerations involved in sharing participant-level clinical research data Wilhelm, E. E., Oster, E., & Shoulson, I. (2014). Approaches and Costs for Sharing Clinical Research Data. *JAMA 311:*1201-1202	This study provided evidence based analysis for policy makers on the economic impact of data sharing, and its impact on drug development.
Pharmacogenomic characterization of gemcitabine response	Analyzed association of variants of genes encoding drug transporters with both gemcitabine cytoxicity and patient response to this drug to identify variants potentially associated with clinical response Harris, M., Bhuvaneshwar, K., Natarajan, T., Sheahan, L., Wang, D., Tadesse, M. G., ... & Deeken, J. (2014). Pharmacogenomic characterization of gemcitabine response–a framework for data integration to enable personalized medicine. *Pharmacogenetics and genomics,* 24(2), 81.	The ultimate goal of this study would be to aid in the development of predictive models of drug response that would improve treatment options for pancreatic cancer patients.

4. Workshops focusing on regulatory science

FDA Workshops to Advance Regulatory Science (FY 2013-2014)

Title	Date	Link	FDA Priority Area[15]
Brain-Computer Interface Devices for Patients with Paralysis and Amputation	November 21, 2014	www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm410261.htm	4
Regulatory Science Considerations for Software Used in Diabetes Management	November 13, 2014	www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm418080.htm	4
Collaborative Approaches for Medical Device and Healthcare Cybersecurity	October 21-22, 2014	www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm412979.htm	7
MDEpiNet Annual Meeting and Think Tanks	October 14-16, 2014	www.mdepinet.org/wp/index.php/meeting-oct-2014/	5
Additive Manufacturing of Medical Devices: An Interactive Discussion on the Technical Considerations of 3D Printing	October 8-9, 2014	www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm397324.htm	3
FDA's GDUFA Public Hearing on Policy Development	September 17, 2014	www.fda.gov/Drugs/NewsEvents/ucm409381.htm	2, 3, 4, 5, 8
FDA/PQRI Conference on Evolving Product Quality	September 16-17, 2014	www.fda.gov/Drugs/NewsEvents/ucm408073.htm	2
International Medical Device Regulators Forum (IMDRF)	September 15-19, 2014	www.imdrf.org	2, 3
Revamping Microbiological Test Methods for Contact Lenses, Products and Accessories to Protect Health and Ensure Safety	September 12, 2014	www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm409778.htm	4
Methodological Considerations in Evaluation of Cancer as an Adverse Outcome Associated With Use of Non-Oncological Drugs and Biological Products in the Postapproval Setting; Public Meeting; Request for Comments	September, 10-11, 2014	www.fda.gov/Drugs/NewsEvents/ucm401452.htm	5
PDA/FDA Joint Regulatory Conference and TRI Courses-Connecting Regulatory, Quality, Science & Compliance: Assuring Customer-Focused Outcomes Throughout the Product Lifecycle	September 8-10, 2014	www.pda.org/conference/2014-pda-fda-joint-regulatory-conference/home	3
Public Workshop on the Clinical Development of Drugs to Prevent Infections Caused by Staphylococcus Aureus in the Healthcare Setting	September 5, 2014	www.fda.gov/Drugs/NewsEvents/ucm407259.htm	2, 8
Hemostatic Medical Devices for Trauma Use	September 3-4, 2014	www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm396497.htm	7

Title	Date	Link	FDA Priority Area[15]
Public Workshop - The Development of New Antibacterial Products: Charting a Course for the Future (co-sponsored by FDA and NIH).	July 30-31, 2014	www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/AboutMCMi/ucm403009.htm	2
Proteomics in the Clinic	June 13, 2014	www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm392858.htm	2, 4
Public Meeting on Inborn Errors of Metabolism Patient-Focused Drug Development	June 10, 2014	www.fda.gov/Drugs/NewsEvents/ucm387057.htm	8
Public Workshop: Immune Responses to Enzymes Replacement Therapies: Role of Immune Tolerance Induction.	June 9, 2014	www.fda.gov/Drugs/NewsEvents/ucm392641.htm	2
Public Workshop: "Advancing the Development of Pediatric Therapeutics (ADEPT): Pediatric Bone Health." Pediatric and Maternal Health Staff in the Center for Drug Evaluation and Research and the Office of Pediatric Therapeutics are announcing a 1-day public workshop	June 3, 2014	www.fda.gov/Drugs/NewsEvents/ucm391538.htm	1, 2
Third Annual ISPE/FDA Current Good Manufacturing Practices Conference	June 2 – 4, 2014	www.fda.gov/Drugs/NewsEvents/ucm398328.htm	3
Study Approaches and Methods To Evaluate the Safety of Drugs and Biological Products During Pregnancy in the Post-Approval Setting; Public Meeting, Request for Comments	May 28-29, 2014	www.fda.gov/Drugs/NewsEvents/ucm386560.htm	5
Postmarketing Requirements for the Class-Wide Extended-Release/Long-Acting Opioid Analgesics	May 19-20, 2014	www.fda.gov/Drugs/NewsEvents/ucm384489.htm	5, 8
Next-Generation Sequencing Technology, Data Formats Standardization and Promotion of Interoperability Protocols	May 19, 2014	www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm227840.htm	4
FY 2014 Regulatory Science Initiatives Part 15 Public Meeting	May 16, 2014	www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm387358.htm	8
Proposed Risk-Based Regulatory Framework and Strategy for Health Information Technology	May 13-15, 2014	www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm392877.htm	4, 5
Public Meeting on Pulmonary Arterial Hypertension Patient-Focused Drug Development	May 13, 2014	www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm379694.htm	8
Synergizing Efforts in Standards Development for Cellular Therapies and Regenerative Medicine Products	April 16, 2014	www.fda.gov/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/ucm364114.htm	4

Title	Date	Link	FDA Priority Area[15]
Methods for Thrombogenicity Testing	April 14, 2014	www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm387409.htm	1, 4
Advancing Regulatory Science for High Throughput Sequencing Devices for Microbial Identification and Detection of Antimicrobial Resistance Markers	April 1, 2014	www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm386967.htm	4
Public Hearing on the Food and Drug Administration Safety and Innovation Act (FDASIA) Section 907	April, 1, 2014	www.fda.gov/Drugs/NewsEvents/ucm389245.htm	5, 8
FDA/AAO Workshop on Developing Novel Endpoints for Premium Intraocular Lenses	March 28, 2014	www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm365646.htm	3
Medical Devices Regulatory Capacity Building Training Program for AHWP, ASEAN, Latin American and Other Medical Devices Regulators	March 27-28, 2014	www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm383690.htm	4
Rescheduled Public Meeting on Fibromyalgia Patient-Focused Drug Development	March 26, 2014	www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm363203.htm	8
Regulatory Science and Sustainable Implementation of National and International Medical Device Registries	March 24, 2014	www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm385887.htm	5
Food and Drug Administration/Xavier University PharmaLink Conference—Leadership in a Global Supply Chain	March 19-20, 2014	http://www.fda.gov/Drugs/NewsEvents/ucm386630.htm	3
Public Workshop: Application of Physiologically –Based Pharmacokinetic Modeling to Support Dose Selection	March 10, 2014	www.fda.gov/Drugs/NewsEvents/ucm387698.htm	2
Over-the-Counter Ophthalmic Drug Products – Emergency Use Eyewash Products; Announcement of Public Hearing; Request for Comments,	March 7, 2014	www.fda.gov/Drugs/NewsEvents/ucm356526.htm	3
IOM/FDA Public Workshop: Characterizing and Communicating Uncertainty in the Assessment of Benefits and Risks	February 12-13, 2014	www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm378861.htm	8
Strategies To Address Hemolytic Complications of Immune Globulin Infusions	February 12, 2014	www.fda.gov/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/ucm378388.htm	2, 4
Public Meeting on Sickle Cell Disease Patient-Focused Drug Development,	February 7, 2014	www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm370867.htm	8
Nanomaterial Drug Products: Current Experience and Management of Potential Risks	January 14-15, 2014	www.fda.gov/Drugs/NewsEvents/ucm376757.htm	3

Title	Date	Link	FDA Priority Area[15]
Sentinel Initiative Public Workshop	January 14, 2014	http://www.brookings.edu/events/2014/01/14-sentinel-initiative-public-workshop	5
Public Workshop – Complex Issues in Developing Drug and Biological Products for Rare Diseases	January 6-7, 2014	www.fda.gov/Drugs/NewsEvents/ucm367820.htm	2
Public Meeting on Fibromyalgia Patient-Focused Drug Development	December 10, 2013	www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm363203.htm	8
Medical Gas Regulation Review; Announcement of Public Meeting	December 6, 2013	www.fda.gov/Drugs/NewsEvents/ucm370351.htm	3
Public Meeting on Meta-Analyses of Randomized Controlled Clinical Trials for the Evaluation of Risk to Support Regulatory Decisions	November 25, 2013	www.fda.gov/Drugs/NewsEvents/ucm370686.htm	5
Public Workshop on Clinical Trial Design for Intravenous Fat Emulsion	October 29, 2013	www.fda.gov/Drugs/NewsEvents/ucm369044.htm	2
Public Workshop on Gastroenterology Regulatory Endpoints and the Advancement of Therapeutics (GREAT II)	October 21 - 22, 2013	www.fda.gov/Drugs/NewsEvents/ucm362766.htm	2
Summit on Healthcare Technology in Non Clinical Settings	October 9-10, 2013	www.aami.org/summit2013	3, 4
Public Workshops on Proactive Compliance, Process Validation and Contract Manufacturing Operation	October 7-10, 2013	www.fda.gov/Drugs/NewsEvents/ucm369798.htm	3
Abuse Deterrent Formulation Science Meeting	September 30-October 1, 2013	www.fda.gov/Drugs/NewsEvents/ucm369998.htm	8
Public Meeting on Narcolepsy Patient-Focused Drug Development	September 24, 2013	www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm359018.htm	8
Synergizing Efforts in Standards Development for Cellular Therapies and Regenerative Medicine Products	September 19, 2013	www.fda.gov/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/ucm364114.htm	4
The Patient Preference Initiative: Incorporating Patient Preference Information into the Medical Device Regulatory Process	September 18-19, 2013	www.fda.gov/medicaldevices/newsevents/workshopsconferences/ucm361864.htm	5
Public Workshop on the Trial Designs and Endpoints for Liver Disease Secondary to Nonalcoholic Fatty Liver Disease (NAFLD)	September 5-6, 2013	www.fda.gov/Drugs/NewsEvents/ucm361439.htm	2
Battery-Powered Medical Devices Workshop: Challenges and Opportunities	July 30-31, 2013	www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm355183.htm	4
Clinical Development Programs for Opioid Conversion; Public Workshop	July 29, 2013	www.fda.gov/Drugs/NewsEvents/ucm340470.htm	8
Public Meeting: Standardizing and Evaluating Risk Evaluation and Mitigation Strategies	July 25-26, 2013	www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm351029.htm	5, 8

Title	Date	Link	FDA Priority Area[15]
Public Workshop on Rechanneling the Current Cardiac Risk Paradigm: Arrhythmia Risk Assessment During Drug Development without the Thorough QT Study	July 23, 2013	www.fda.gov/Drugs/NewsEvents/ucm358205.htm	1
Public Meeting on Lung Cancer Patient-Focused Drug Development	June 28, 2013	www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm353273.htm	8
The Center for Devices and Radiological Health (CDRH) Health of Women (HoW) Program Launch: Educate, Enable, Enlist and Explore - How to Improve the Health of Women	June 24-25, 2013	www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm346073.htm	2, 8
Generic Drug User Fee Amendments of 2012; Regulatory Science Initiatives (Part 15 Public Meeting)	June 21, 2013	www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm353273.htm	8
CDER Forum for International Drug Regulatory Authorities	June 17-21, 2013	www.fda.gov/Drugs/NewsEvents/ucm337022.htm	2, 5
CDER Forum for International Drug Regulatory Authorities	June 17, 2013	www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm353273.htm	8
Public Meeting on HIV Patient-Focused Drug Development and HIV Cure Research	June 14, 2013	www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm348598.htm	8
FDA/NIH/NSF Workshop on Computer Models and Validation for Medical Devices	June 11-12, 2013	www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm346375.htm	3, 4
Fecal Microbiota for Transplantation	June 7, 2013	www.fda.gov/BiologicsBloodVaccines/NewsEvents/WorkshopsMeetingsConferences/ucm341643.htm	4
Summit on Color in Medical Imaging	May 8-9, 2013	www.color.org/events/medical/medical_summit_2013.xalter	4
FDA Public Workshop: Clinical Trial Design Issues - Development of New Therapies for Non-Muscle Invasive Bladder Cancer	May 6, 2013	www.fda.gov/Drugs/NewsEvents/ucm348373.htm	2
FDA Public Workshop: Clinical Trial Design Issues - Drug & Device Development for Localized Prostate Cancer	May 5, 2013	www.fda.gov/Drugs/NewsEvents/ucm348372.htm	2
Accessible Medical Device Labeling in a Standard Content and Format	April 29-30, 2013	www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm334501.htm	8
Home Use of Diabetes and Cardiovascular Medical Devices	April 23, 2013	www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm346167.htm	8
International Consortium of Cardiovascular Registries	April 22, 2013	www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm344597.htm	5
FDA Public Workshop, Innovations in Breast Cancer Drug Development – Neoadjuvant Breast Cancer Workshop	March 22, 2013	www.fda.gov/Drugs/NewsEvents/ucm339396.htm	2

Title	Date	Link	FDA Priority Area[15]
Public Workshop on Minimal Residual Disease (MRD) as a Surrogate Endpoint in Acute Myeloid Leukemia (AML)	March 4, 2013	www.fda.gov/Drugs/NewsEvents/ucm341421.htm	1, 2
Public Workshop on Minimal Residual Disease (MRD) as a Surrogate Endpoint in Chronic Lymphocytic Leukemia (CLL)	February 27, 2013	www.fda.gov/Drugs/NewsEvents/ucm340707.htm	1, 2
Improved Access to Device Information: What a UDI System can do for Patients and Consumers	February 26, 2013	www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm338201.htm	5
Clinical Flow Cytometry in Hematologic Malignancies	February 25-26, 2013	www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm334772.htm	2
Clinical Development Programs for Disease-Modifying Agents for Peripheral Neuropathy	February 11-12, 2013	www.fda.gov/drugs/newsevents/ucm310416.htm	2
Impact of Approved Drug Labeling on Chronic Opioid Therapy (Part 15 Meeting)	February 7-8, 2013	www.fda.gov/Drugs/NewsEvents/ucm326450.htm	8
Creating an Alternative Approval Pathway for Certain Drugs Intended to Address Unmet Medical Need (Public Hearing)	February 4-5, 2013	www.fda.gov/Drugs/NewsEvents/ucm335680.htm	2
Sentinel Initiative Public Workshop	January 31, 2013	http://www.brookings.edu/events/2013/01/31-sentinel-public-workshop	5
FDA Webinar: New Draft Guidance on "FDA Guidance for Industry Webinar on Draft Guidance Vaginal Microbicides: Development for the Prevention of HIV Infection"	January 22, 2013	www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/ucm227840.htm.	4

ii. Adopting and Incorporating Regulatory Science

1. Scientific training and professional development activities (FY 2014)

Due to the rapid pace of advance in the disciplines that underlie medical development, FDA reviewers and staff must continually update their scientific expertise. This occurs through dedicated course offerings, symposia dedicated to specific issues in regulatory science, intramural journal clubs and seminars, and conferences where FDA scientists present their work to the research community. Although a complete compilation of such training activities in beyond the scope of this report, the following table presents some specific examples from FY 2014.

Multisession Course Offerings in Regulatory Science (FY 2014)

Advanced Science Offerings that Consisted of Multiple Sessions in FY 2014	Offerings (Classes/Lectures per Offering)
CDRH Journal Club	2 (13)
Infectious Disease Journal Club	2 (32)
CDER Scientific Rounds	1 (18)
CDER Scientific Seminars	1 (17)
University Programs	1 (4)
Statistics for Diagnostic Devices	1 (8)
The Retinal Implants Series	1 (5)
Epidemiology Grand Rounds (devices)	1 (6)
CBER Journal Club	1 (5)
CDER Science Day	1 (30)
CDRH Journal Club	2 (13)
Foundations of Pre-Clinical Review Lecture Series	2 (5)
Infectious Disease Journal Club	2 (32)
Medical Countermeasures Lecture Series	1 (5)
Medical Officer Rounds: Gastroenterology and Inborn Errors Products	1 (8)
MCMi Regulatory Science Symposium	1 (25)
Epidemiology in Drug Safety	1 (9)
Pediatric Orthopedics	1 (5)

Processes that specifically target the evaluation of new science.

Metric – list and describe the FDA's formal processes for evaluating new science for its applicability to regulatory decision making. Where meaningful, include quantitative submission metrics

- Development and Updating of Guidance
  Metric – list new and revised guidance documents that integrate new science and include and explain of their significance for medical product development and review
- Advisory committee meetings
  Metric – enumerate and summarize advisory committee meetings with a focus on the application of new science to regulatory decision making
- Consultations with International Regulators
  Metric – enumerate and summarize meetings with International Regulators
- Regulatory actions prompted by new science, such as communications with patients, prescribers and health care professionals

- Strategy and Implementation Plan p. 45

2. Recent guidances that address emerging regulatory science

The development and issuing of guidance documents is a critical part of FDA's regulatory science activities. Advances in emerging sciences inevitably pose complex issues in regulatory science: How should a new drug be evaluated based on post-marketing evidence for similar drugs? What standards should govern new kinds of data generated by novel technologies? Under what conditions can a new clinical trial design be integrated into the clinical assessment of a new drug candidate? The guidance that FDA provides on these issues and a multitude of others raised by continual scientific discovery helps to ensure consistency in the regulatory setting and provides needed clarity to industry to foster product development. Excluded from the following list of guidance documents for 2013 and 2014 are those focused on bioequivalence recommendations for a single product. These can be found at www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075207.htm.

FDA Guidance Documents from Medical Product Centers Focusing on General Topics in Regulatory Science (FY 2013 and 2014)

Guidance	Date	Link	FDA priority[15]
Migraine: Developing Drugs for Acute Treatment	October 21, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM419465.pdf	2
Flow Cytometric Devices - Draft Guidance for Industry and Food and Drug Administration Staff	October 14, 2014	www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM418205.pdf	4
Over-the-Counter Pediatric Liquid Drug Products Containing Acetaminophen	October 7, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM417568.pdf	1, 8
Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval	October 6, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM305501.pdf	2
Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories - Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)	October 2, 2014	www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM416685.pdf	4
Evaluation of Sex-Specific Data in Medical Device Clinical Studies - Guidance for Industry and Food and Drug Administration Staff	August 22, 2014	www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM283707.pdf	2

Guidance	Date	Link	FDA priority[15]
FDA Decisions for Investigational Device Exemption Clinical Investigations - Guidance for Sponsors, Clinical Investigators, Institutional Review Boards, and Food and Drug Administration Staff	August 19, 2014	www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279107.pdf	2
Unique Device Identification System: Small Entity Compliance Guide - Guidance for Industry and Food and Drug Administration Staff	August 13, 2014	www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM409401.pdf	3
Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products—Considerations, Content and Format	August 13, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM109739.pdf	8
Immunogenicity Assessment for Therapeutic Protein Products	August 13, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338856.pdf	1, 2
In Vitro Companion Diagnostic Devices - Guidance for Industry and Food and Drug Administration Staff	August 8, 2014	www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf	4
In Vitro Companion Diagnostic Devices; Guidance for Industry and FDA Staff	August 6, 2014	www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf	4
Design Considerations for Devices Intended for Home Use - Guidance for Industry and Food and Drug Administration Staff	August 5, 2014	www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM331681.pdf	8
Upper Facial Lines: Developing Botulinum Toxin Drug Products	August 5, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM407983.pdf	2
The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)] - Guidance for Industry and Food and Drug Administration Staff	July 28, 2014	www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM284443.pdf	4
Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications	July 25, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333969.pdf	2
Benefit-Risk Factors to Consider When Determining Substantial Equivalence in Premarket Notifications [510(k)] with Different Technological Characteristics: Draft Guidance for Industry and Food and Drug Administration Staff13	July 15, 2014	www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm282958.htm	2

Guidance	Date	Link	FDA priority[15]
Reporting Drug Sample Information Under Section 6004 of the Affordable Care Act	July 10, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM404473.pdf	3
Neglected Tropical Diseases of the Developing World: Developing Drugs for Treatment or Prevention	July 3, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269221.pdf	2, 7
Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act	July 1, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM403496.pdf	3
Global Unique Device Identification Database; Guidance for Industry and Food and Drug Administration Staff	June 27, 2014	www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM369248.pdf	4
Guidance for Industry: Considering Whether a Food and Drug Administration-Regulated Product Involves the Application of Nanotechnology	June 27, 2014	www.fda.gov/RegulatoryInformation/Guidances/ucm257698.htm	4
Medical Device Data Systems, Medical Image Storage Devices, and Medical Image Communication Devices; Draft Guidance for Industry and Food and Drug Administration Staff	June 25, 2014	www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM401996.pdf	5
Uncomplicated Gonorrhea: Developing Drugs for Treatment	June 18, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM401620.pdf	2
Internet/Social Media Platforms with Character Space Limitations—Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices	June 17, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM401087.pdf	8
Internet/Social Media Platforms: Correcting Independent Third-Party Misinformation About Prescription Drugs and Medical Devices	June 17, 2014	www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm401079.pdf	8
Q4B: Annex 6: Uniformity of Dosage Units General Chapter	June 13, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM085364.pdf	3
Providing Submissions in Electronic Format — Postmarketing Safety Reports	June 9, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072369.pdf	5
Expedited Programs for Serious Conditions—Drugs and Biologics	May 30, 2014	https://www.federalregister.gov/articles/2014/05/30/2014-12534/guidance-for-industry-on-expedited-programs-for-serious-conditions-drugs-and-biologics-availability	2,4

Guidance	Date	Link	FDA priority[15]
Product Development Under the Animal Rule	May 29, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM399217.pdf	7
Best Practices in Developing Proprietary Names for Drugs	May 28, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf	8
ANDAs: Stability Testing of Drug Substances and Products, Questions and Answers	May 14, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM366082.pdf	3
Appropriate Use of Voluntary Consensus Standards in Premarket Submissions for Medical Devices - Draft Guidance for Industry and Food and Drug Administration Staff15	May 13, 2014	www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm396209.htm	2
Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product	May 13, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM397017.pdf	4
Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia: Developing Drugs for Treatment	May 6, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM234907.pdf	2
Surveying, Leveling, or Alignment Laser Products; Draft Guidance for Industry and Food and Drug Administration Staff	May 5, 2014	www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm392707.htm	3
Providing Information about Pediatric Uses of Medical Devices - Guidance for Industry and Food and Drug Administration Staff	May 1, 2014	www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm339162.htm	8
Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions - Draft Guidance for Industry and Food and Drug Administration Staff	April 23, 2014	www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm393879.htm	2
Interpreting Sameness of Monoclonal Antibody Products Under the Orphan Drug Regulations	April 22, 2014	www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM170111.pdf	4
Live Case Presentations During Investigational Device Exemption Clinical Trials; Draft Guidance for Institutional Review Boards, Industry, Investigators, and Food and Drug Administration Staff	April 17, 2014	www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm392728.htm	4

Guidance	Date	Link	FDA priority[15]
Endotoxin Testing Recommendations for Single-Use Intraocular Ophthalmic Devices; Draft Guidance for Industry and Food and Drug Administration Staff	April 17, 2014	www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm393374.htm	1,4
Immunogenicity-Related Considerations for the Approval of Low Molecular Weight Heparin for NDAs and ANDAs	April 8, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM392194.pdf	1, 3
Premarket Assessment of Pediatric Medical Devices - Guidance for Industry and Food and Drug Administration Staff	March 24, 2014	www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089740.htm	2
Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway	March 24, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM390058.pdf	8
Humanitarian Device Exemption (HDE): Questions and Answers - Draft Guidance for HDE Holders, Institutional Review Boards, Clinical Investigators, and Food and Drug Administration Staff	March 18, 2014	www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm389154.htm	2
Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products	March 13, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM389069.pdf	3
Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: Developing Drug Products for Treatment	March 10, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM388568.pdf	2
Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency: Guidance for Submitting HIV-1 Resistance Data: Attachment to the Guidance	February 27, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM387446.pdf	2
E2B(R3) Electronic Transmission of Individual Case Safety Reports Implementation Guide — Data Elements and Message Specification; and Appendix to the Implementation Guide — Backwards and Forwards Compatibility	February 21, 2014	www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm274966.htm	5
Analytical Procedures and Methods Validation for Drugs and Biologics (PDF - 359KB)	February 19, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM386366.pdf	3
Providing Regulatory Submissions in Electronic Format--Receipt Date	February 10, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072385.pdf	2

Guidance	Date	Link	FDA priority[15]
Providing Submissions in Electronic Format -- Standardized Study Data	February 5, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf	2
Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act	February 5, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM384686.pdf	2
Analgesic Indications: Developing Drug and Biological Products	February 5, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM384691.pdf	2
Qualification Process for Drug Development Tools	February 1, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf	2, 4
Medical Devices Containing Materials Derived From Animal Sources (Except for In Vitro Diagnostic Devices); Draft Guidance for Industry and Food and Drug Administration Staff	January 23, 2014	www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM381491.pdf	3
Reporting of Computational Modeling Studies in Medical Device Submissions; Draft Guidance for Industry and Food and Drug Administration Staff	January 17, 2014	www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm371016.htm	5
Fulfilling Regulatory Requirements for Postmarketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics	January 13, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM381352.pdf	8
Qualification Process for Drug Development Tools: (Attachment) Qualification of Exacerbations of Chronic Pulmonary Disease Tool for Measurement of Symptoms of Acute Bacterial Exacerbation of Chronic Bronchitis in Patients With Chronic Obstructive Pulmonary Disease	January 9, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM380961.pdf	2, 4
Community-Acquired Pneumonia — Developing Antimicrobial Drugs for Treatment	January 9, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM123686.pdf	2
Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use; Draft Guidance for Industry and Food and Drug Administration Staff	January 7, 2014	www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM380325.pdf	2

Guidance	Date	Link	FDA priority[15]
Self-Monitoring Blood Glucose Test Systems for Over-the-Counter Use; Draft Guidance for Industry and Food and Drug Administration Staff	January 7, 2014	www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM380327.pdf	2
Qualification Process for Drug Development Tools	January 6, 2014	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf	2, 4
Naming of Drug Products Containing Salt Drug Substances	December 24, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM379753.pdf	8
Size, Shape, and Other Physical Attributes of Generic Tablets and Capsules	December 9, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377938.pdf	8
Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application	December 4, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377465.pdf	2
Product Name Placement, Size, and Prominence in Advertising and Promotional Labeling	November 18, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070076.pdf	8
Medical Device Development Tools; Draft Guidance for Industry, Tool Developers, and Food and Drug Administration Staff	November 14, 2013	www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm374427.htm	2
Design Considerations for Pivotal Clinical Investigations for Medical Devices - Guidance for Industry, Clinical Investigators, Institutional Review Boards and Food and Drug Administration Staff	November 7, 2013	www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm373750.htm	3
Pulmonary Tuberculosis: Developing Drugs for Treatment	November 5, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM373580.pdf	2, 7
Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment	October 16, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071185.pdf	2, 7
Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment	October 16, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225333.pdf	2
Q4B Annex 14: Bacterial Endotoxins Test General Chapter	October 15, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM219167.pdf	1, 3
Q3D Elemental Impurities	October 15, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM371025.pdf	3

Guidance	Date	Link	FDA priority[15]
Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies - Guidance for Industry and Food and Drug Administration Staff	October 1, 2013	www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279103.pdf	2
Mobile Medical Applications - Guidance for Industry and Food and Drug Administration Staff	September 25, 2013	www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM263366.pdf	5, 8
Endocrine Disruption Potential of Drugs: Nonclinical Evaluation3	September 19, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM369043.pdf	1
Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products — Content and Format	September 17, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368602.pdf	8
Bioanalytical Method Validation [Revised Final]	September 12, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf	3
Investigational New Drug Applications (INDs)-Determining Whether Human Research Studies Can Be Conducted Without an IND	September 10, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM229175.pdf	2
The Applicability of Good Laboratory Practice in Premarket Device Submissions: Questions and Answers - Draft Guidance for Industry and Food and Drug Administration Staff	August 28, 2013	www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm366338.htm	3
Radio Frequency Wireless Technology in Medical Devices - Guidance for Industry and Food and Drug Administration Staff	August 14, 2013	www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm077210.htm	4
Safety Labeling Changes -- Implementation of Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act	July 30, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM250783.pdf	8
Providing Submissions in Electronic Format – Postmarket Non-Expedited ICSRs Technical Questions and Answers	July 24, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM362174.pdf	5
Antibacterial Therapies for Patients With Unmet Medical Need for the Treatment of Serious Bacterial Diseases	July 1, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM359184.pdf	2, 7

Guidance	Date	Link	FDA priority[15]
Implanted Blood Access Devices for Hemodialysis; Draft Guidance for Industry and Food and Drug Administration Staff	June 28, 2013	www.fda.gov/RegulatoryInformation/Guidances/ucm302589.htm	4
Heparin for Drug and Medical Device Use: Monitoring Crude Heparin for Quality	June 25, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291390.pdf	3
ANDAs: Stability Testing of Drug Substances and Products	June 18, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320590.pdf	3
Content of Premarket Submissions for Management of Cybersecurity in Medical Devices; Draft Guidance for Industry and Food and Drug Administration Staff	June 14, 2013	www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm356186.htm	4
Codevelopment of Two or More New Investigational Drugs for Use in Combination	June 14, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf	2, 4
Expedited Programs for Serious Conditions—Drugs and Biologics; Draft Guidance for Industry	June 6, 2013	https://www.federalregister.gov/articles/2013/06/26/2013-15250/draft-guidance-for-industry-on-expedited-programs-for-serious-conditions-drugs-and-biologics	2, 4
Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment	June 4, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM355128.pdf	2
Rheumatoid Arthritis: Developing Drug Products for Treatment	May 30, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM354468.pdf	2
Q4B Annex 13: Bulk Density and Tapped Density of Powders General Chapter	May 24, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM218825.pdf	3
Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets	May 14, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf	5
Assay Migration Studies for In Vitro Diagnostic Devices - Guidance for Industry and FDA Staff	April 25, 2013	www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM092752.pdf	3
Regulatory Classification of Pharmaceutical Co-Crystals	April 25, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM281764.pdf	3
Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors	April 23, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf	8
Self-Selection Studies for Nonprescription Drug Products	April 10, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM272122.pdf	8

Guidance	Date	Link	FDA priority[15]
Molecular Diagnostic Instruments with Combined Functions - Draft Guidance for Industry and Food and Drug Administration Staff	April 9, 2013	www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm346189.htm	4
Providing Postmarket Periodic Safety Reports in the ICH E2C(R2) Format (Periodic Benefit-Risk Evaluation Report)	April 5, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346564.pdf	5
Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4 - Draft Guidance for Industry and FDA Staff	April 1, 2013	www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM346181.pdf	3
Guidance for Industry and Food and Drug Administration Staff: Investigational Device Exemption Guidance for Retinal Prostheses	March 6, 2013	www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm341954.htm	4
Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling Good Review Practice	February 27, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM341394.pdf	8
Labeling for Human Prescription Drug and Biological Products - Implementing the PLR Content and Format Requirements	February 22, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075082.pdf	8
Antiviral Product Development — Conducting and Submitting Virology Studies to the Agency Guidance for Submitting HCV Resistance Data - Attachment to Guidance	February 22, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM340712.pdf	2
Alzheimer's Disease: Developing Drugs for the Treatment of Early Stage Disease	February 7, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338287.pdf	2
S10 Photosafety Evaluation of Pharmaceuticals	February 1, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM337572.pdf	2
Clinical Pharmacogenomics: Premarket Evaluation in Early-Phase Clinical Studies and Recommendations for Labeling	January 29, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM337169.pdf	2, 4
E3 Structure and Content of Clinical Study Reports - Questions and Answers (R1)	January 25, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM336889.pdf	2
Humanitarian Use Device (HUD) Designations - Guidance for Industry and FDA Staff	January 24, 2013	www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM336515.pdf	2

Guidance	Date	Link	FDA priority[15]
Abuse-Deterrent Opioids-Evaluation and Labeling 1	January 9, 2013	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM334743.pdf	1, 2
Safety Reporting Requirements for INDs and BA/BE Studies- Small Entity Compliance Guide 18	December 19, 2012	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332846.pdf	2
Safety Reporting Requirements for INDs (Investigational New Drug Applications) and BA/BE (Bioavailability/Bioequivalence) Studies 16	December 19, 2012	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf	2
Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning 14	December 18, 2012	www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf	2
Guidance for Industry: Providing Submissions in Electronic Format -- Summary Level Clinical Site Data for CDER 13	December 18, 2012	www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf	2
Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products 36	December 14, 2012	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332181.pdf	2
Draft Guidance for Industry and Food and Drug Administration Staff; Design Considerations for Devices Intended for Home Use	December 13, 2012	www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm331675.htm	3
Safety Considerations for Product Design to Minimize Medication Errors	December 12, 2012	www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm331808.htm	1, 8
Labeling and Effectiveness Testing: Sunscreen Drug Products for Over-The-Counter Human Use — Small Entity Compliance Guide 17	December 5, 2012	www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm330694.htm	8
Limiting the Use of Certain Phthalates as Excipients in CDER-Regulated Products	December 5, 2012	www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm330792.htm	1, 3
Investigational New Drug Applications for Positron Emission Tomography (PET) Drugs 61	December 3, 2012	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291573.pdf	4
Guidance for Industry and Food and Drug Administration Staff; The Content of Investigational Device Exemption and Premarket Approval Applications for Artificial Pancreas Device Systems	November 23, 2012	www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM259305.pdf	4
Vaginal Microbicides: Development for the Prevention of HIV Infection	November 21, 2012	www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm328834.htm	2

Guidance	Date	Link	FDA priority[15]
Q11 Development and Manufacture of Drug Substances	November 19, 2012	www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM261078.pdf	3
Labeling for Bronchodilators: Cold, Cough, Allergy, Bronchodilator, And Antiasthmatic Drug Products for Over-the-Counter Human Use (Small Entity Compliance Guide)	November 14, 2012	www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm327834.htm	8
Draft Guidance for Industry and Food and Drug Administration Staff; Highly Multiplexed Microbiological/Medical Countermeasure In Vitro Nucleic Acid Based Diagnostic Devices	November 9, 2012	www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm327293.htm	7
E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs - Questions and Answers (R1)	October 12, 2012	www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm323656.htm	2
Guidance for Industry Acute Bacterial Sinusitis: Developing Drugs for Treatment	October 5, 2012	www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm322630.htm	2
Guidance for Industry: Acute Bacterial Otitis Media: Developing Drugs for Treatment	October 1, 2012	www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm323763.htm	2

3. Advisory committee meetings devoted to general topics in regulatory science

Advisory committees – generally consisting of a chair, several members with scientific and medical expertise, plus consumer, industry, and sometimes patient representatives – provide FDA with independent advice on a variety of regulatory questions that are driven by scientific advances. These committees address not only scientific questions related to specific applications for drugs, biologics, and devices, but also general questions posed by emerging sciences. Like guidance documents, they are key avenues through which FDA incorporates and adopts scientific advances into its regulatory decision making and communicates with industry on emerging scientific issues. Recent examples are listed below.

Recent Advisory Committee Meetings Devoted to

Medical Product Development and the Topics Addressed

Advisory Committee(s)	Date	Topic(s) Addressed
Pharmaceutical Science and Clinical Pharmacology	September 15, 2013	Optimal strategies for the evaluation, interpretation, and communication of drug-drug interaction (DDI) information, including (1) Best practices in DDI communication through prescription drug product labels (2) appropriate criteria for determining whether or not to describe DDI information derived from the literature in product labels; and (3) how package insert information on DDIs is used by various end-users in decision making and/or communication
Joint meeting: Medical Imaging Drugs-Oncologic Drugs	May 13, 2013	The safety and efficacy of currently approved leukocyte growth factors (LGFs) as potential treatments for radiation-induced myelosuppression associated with a radiological/nuclear incident
Joint meeting: Arthritis and Drug Safety and Risk Management	February 10-11, 2014	Data and analyses published in 2006 or later that are relevant to further understanding the relationship between nonsteroidal anti-inflammatory drugs (NSAIDs) and cardiovascular thrombotic risk that is currently described in NSAID class labeling.
Cellular, Tissue, and Gene Therapy	February 26, 2014	Considerations for the design of early-phase clinical trials of cellular and gene therapy products.
Anti-infective Drugs	March 31, 2014	Development programs for antibacterial drugs to fulfill an unmet medical need for the treatment of serious bacterial diseases.
Nonprescription drugs	September 4-5, 2014	The scope of safety testing that should be required for active ingredients to be marketed in U.S. over-the-counter (OTC) sunscreen products.
Reproductive Health Drugs- Drug Safety Risk Management	September 17, 2014	The efficacy and safety (testosterone undecanoate) intramuscular injection, for replacement therapy in adult males for conditions associated with a deficiency or absence of testosterone

4. Examples of communications and regulatory actions prompted by new science

Recent Drug information Round Videos and Drug Safety Communications

Communication	Date
Drug Information Round Videos	
Traveling with Prescription Medications	August 2014
Managing Drug Shortages	July 2014
Electronic Orange Book	March 2014
Drug Promotion	October 2013
Drug Name Review	September 2013
Communicating Benefit Risk Information	August 2013
Drug Safety Communications	

Communication	Date
FDA Drug Safety Communication: FDA approves label changes for asthma drug Xolair (omalizumab), including describing slightly higher risk of heart and brain adverse events1	September 26, 2014
FDA Drug Safety Communication: FDA recommends not using lidocaine to treat teething pain and requires new Boxed Warning	September, 2014
FDA warns of rare but serious hypersensitivity reactions with certain over-the-counter topical acne products	June 25, 2014
FDA review of cardiovascular risks for diabetics taking hypertension drug olmesartan not conclusive; label updates required	June 24, 2014
FDA warns that cancer drug docetaxel may cause symptoms of alcohol intoxication after treatment	June 20, 2014
FDA adding general warning to testosterone products about potential for venous blood clots	June 19, 2014
FDA warns of next-day impairment with sleep aid Lunesta (eszopiclone) and lowers recommended dose	May 15, 2014
PRISM study on TIV and febrile seizures in children	May 14, 2014
FDA study of Medicare patients finds risks lower for stroke and death but higher for gastrointestinal bleeding with Pradaxa (dabigatran) compared to warfarin	May 13, 2014
FDA requires label changes to warn of rare but serious neurologic problems after epidural corticosteroid injections for pain	April 23, 2014
FDA is Working Closely with Manufacturers of Meningitis B Vaccines	April 7, 2014
FDA clarifies Warning about Pediatric Use of Revatio (sildenafil) for Pulmonary Arterial Hypertension	March 31, 2014
FDA approves label changes for antibacterial Doribax (doripenem) describing increased risk of death for ventilator patients with pneumonia	March 6, 2014
FDA to review heart failure risk with diabetes drug saxagliptin (marketed as Onglyza and Kombiglyze XR)	February 11, 2014
FDA evaluating risk of stroke, heart attack and death with FDA-approved testosterone products	January 31,2014
FDA warns of possible harm from exceeding recommended dose of over-the-counter sodium phosphate products to treat constipation	January 8, 2014
Safety communication-new boxes warning for IGIV and thrombosis	November 14, 2013
FDA approves label change for drugs containing olmesartan medoxomil for risk of sprue-like enteropathy based in part on Mini-Sentinel data	July 3, 2013
Mini-Sentinel PRISM on rotavirus and intussesception	June 13, 2013
Safety communication on thrombosis and hemolysis and IGIV	November 13, 2012

VI. Building Infrastructure to Advance the Goals of the User Fee Agreements

Building Infrastructure to Evaluate Emerging Science and Technology

• Developing and/or integrating new data standards and software tools for data receipt, analysis, evaluation, and visualization to facilitate efficient, effective and consistent review of complex data

Metric – list and provide brief description of significant new programs that include the development of data standards or reviewers software tools. Include indicators of adoption of these approaches by regulated industry.

• IT hardware for data receipt management and storage, e.g. next generation sequencing data storage, transfer, analysis

Metric – list and provide brief description of significant new IT investments that enable improved receipt and storage a data while enhancing the effectiveness of data standards and software.

• Research Infrastructure – investments in key novel technologies to support intramural regulatory science programs in order to prepare for regulatory evaluation of innovative medical products and to enhance evaluation tools available for existing licensed products

Metric – list and briefly describe significant enhancements to the scientific infrastructure and how they are (or will) enhance the ability of the agency to evaluate emerging technologies while improving its ability to respond rapidly to public health emergencies involving regulated products.

Strategy and Implementation Plan, p. 46.

i. Supporting a More Efficient Regulatory Review of Clinical Trial Data

In the last two years, FDA has accelerated its wide-ranging efforts to standardize the vast array of data that it receives (and generates) to make it more informative and accessible to regulators and researchers, and render the data inadequacies more apparent. This process of data standardization is supporting a rapidly expanding array of integrated analytic tools and data systems that support regulatory decision making, e.g., in the review of applications for new drugs, biologics, and generics and in postmarket surveillance of medical products. We summarize at a relatively high level some key accomplishments for FY 2013 and FY 2014 below.

Major accomplishments by FDA toward the goal of standardization of clinical trial data in regulatory submissions were the following:

- Development and publishing of two guidances: 1) A draft guidance on "Providing Regulatory Submissions in Electronic Format—Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act"; and 2) a revised draft of the guidance on "Providing Regulatory Submissions In Electronic Format—Standardized Study Data"

- Publishing of the Study Data Technical Conformance Guide providing specifications, recommendations, and general considerations on how to submit standardized study data using FDA-supported data standards
- Drafting of revisions to the Study Data Standards Resources web pages for ease of use and access to relevant information
- Publishing of a position statement on the use of Système International units for lab tests

And in the area of research and development:

- Development and implementation of a standard procedure to support the testing and acceptance of study data standards
- An internal assessment of the generic drug review process with emphasis on data usage and submission quality to determine areas where standardization could add benefit and an initiation of a review of product quality data to assess consistency and usage and identify steps that would have a positive impact
- Expanding the therapeutic area requirements from four areas to an additional 12 areas
- A initial evaluation of adopting Health and Human Services/Office of the National Coordinator for Health Information Technology (HHS/ONC) meaningful use standards for clinical data used in research
- Evaluation of the CDISC Extensible Markup Language (XML) transport format for the submission of regulatory study data
- Testing and posting results for Study Participation and Patient Narrative HL7 standards
- Collaborating with external stakeholders on the use of semantic web technologies for information modeling and exchange

Significance: All of these initiatives help the FDA realize its ongoing commitment to the development, implementation, and maintenance of a comprehensive data standards program to facilitate the efficient and effective review of regulatory submissions so that safe and effective products are available to the market sooner.

ii. Development and Deployment of Systems and Tools to Support Regulatory Review

FDA inaugurated the Jumpstart service, which applies tools and technologies to NDA or BLA submissions to give reviewers a global view of the submission and data, confidence in the data they have (or an understanding of its inadequacies), support with requests to sponsors when issues that impact review are found.

Significance:

- Jumpstart was used to review 25 new drug applications. Critical issues were communicated to applicants with rapid remediation in some cases.
- The service allows for multiple views of data to improve safety signal identification and hypothesis generation and provides outputs and tools with loaded data to allow drill down on relevant issues throughout the review.

FDA continued to develop, implement, and deploy the Janus Clinical Trial repository, a data warehouse application to enable the reliable validation, transformation, loading, and management of standardized clinical trials data in a secure database, and to support reviewer access to that data using a variety of analysis tools. Recent milestones in the realization of this project include the following:

- Completion of migration of CTR from NCI to FDA's data center
- Completion of requirements gathering, development, testing, and implementation of the core functions of the CTR application, including the ability to load and validate study data into the back-end repository and an analysis-ready database that can be accessed by reviewers using multiple tools, including JReview, SAS, R, JMP, and EmpiricaStudy
- Development testing and implementation of a web application that enables reviewers to run a series of analytical reports that are aligned with the analyses they must perform during their regulatory review activities
- Completion of requirements gathering, prototyping, development, and implementation of "tools" that support data curation, meta-data retrieval and analysis, ad hoc query, and self-service visualization and analytic functions.
- Successful loading of 51 legacy-converted study datasets into the CTR, and integrated JReview to enable reviewer access to the analysis-ready database

Significance: The CTR will have a positive impact on the reviewer's interface with the NDA data submission. The tool will also enable the storing and replication of analyses that are performed in the conduct of review, enabling a "trace back" to the analytic methods. For

prespecified analytic needs with a firm methodological basis, the CTR can enable integration and pooling of trial-level or subject-level data. This can serve the purpose of regulatory research or review of evolving efficacy and safety signals.

FDA implemented Empirica Study (EST), an advanced software application that provides a repeatable analysis environment for drug safety analysis of multiple clinical trial data and pools across applications submitted in conformance with SDTM CDISC data standards. The application:

- Enables rapid loading of large datasets, browsing, and assessment of the data. If the data are provided by the sponsor in full compliance with SDTM CDISC standards, the raw data and a full set of over 6,000 analyses outputs are available for exploration within a day of data receipt. These outputs include interactive graphics that optimize the display of complex temporal patterns in the data and tables linked to a library of state-of-the art statistical methods,
- Generates auditable results that are easily traceable (human-readable). All the results have drill-down functionality to the data behind the results, and are simple to understand and interpret in real time by the multidisciplinary review team, and
- Includes sophisticated analytical methodologies for exploration of potential safety signals. The application is programmed to help reviewers address the 21st Century review process.

Significance:

- This approach reduces or eliminates the need to always have to reconfigure the data and analytical tools for each new analysis or re-analysis.
- Regulators can better assess whether the differences between patients exposed to a treatment compared to patients exposed to a comparator is the result of unbalanced assignments.
- Regulators can make better informed decisions supported by analyzing evidence on harms by different treatment options studied in multiple clinical trials.
- Reviewers can focus on assessing the analytical outputs instead of reconfiguring data and tools as in the past.
- The optimized and comprehensive displays of the data enable reviewers to identify positive and negative safety issues they would be otherwise unaware of.

- Organized information allows better communication among reviewers of different specialties, and needed adjustments to the analytical outputs are done in a more efficient fashion.

The web-based clinical study data review tool JReview was implemented for use by clinical reviewers.

Significance: JReview allows FDA's clinical reviewers to tabulate, visualize, and analyze safety and efficacy data more efficiently and comprehensively.

The MAED (MedDRA Adverse Event Diagnosis) Service was put into production following successful prototyping and enhancements. The Likelihood Ratio Test tool, developed primarily for adverse event signal detection, was recently incorporated into the MAED tool and expands the scope of safety assessments that can be performed with the tool.

Significance: MAED makes it possible to perform over 200 Standardized MedDRA Queries and Adverse Events analyses on all levels of the MedDRA hierarchy in minutes.

FDA expanded the use of Empirica Signal to over 400 individuals.

Significance: Empirica Signal helps to identify new drug safety issues in FDA's FAERS database of adverse event reports submitted by the public, and provides interactive, web-based, data mining graphs that provide context of new drug safety issues.

Mini-Sentinel is a pilot project sponsored by FDA to create an active surveillance system - the Sentinel System - to monitor the safety of FDA-regulated medical products using electronic healthcare data from multiple sources. Mini-Sentinel is part of the FDA's Sentinel Initiative, which is exploring a variety of approaches for improving the Agency's ability to quickly identify and assess safety issues. Key accomplishments for 2014 include the following:

- The Mini-Sentinel Distributed Database (MSDD) was expanded from 130 million patients in December 2012, to more than 153 million patients by September 2013, and to more than 178 million patients by July 2014.
- The Prospective Routine Observational Monitoring Program Tools (PROMPT) was inaugurated. The PROMPT tools complement existing capabilities to query the distributed database using modular programs and customized programming.

Significance: Results generated through queries of the MSDD supported four Drug Safety Communications (DSC) and two product labeling changes during FYs 2013 and 2014. PROMPT will enable prospective and sequential semi-automated surveillance of medical products using a variety of methodologies.

FDA inaugurated the Nonclinical Information Management System – NIMS: Key recent accomplishments include:

- Publication of the Non-Clinical Validation Rules,
- Provision of service to orient non-clinical reviewers to dataset submissions within the NIMS tool and provide real-time training to allow for reviewers to take full advantage of NIMS and standardized data,
- Completion of MCM data model in preparation for the development and implementation of the visualization functionality in a future NIMS release,
- Data Standardization Services,
- Planning and implementation of a secure external Data Standardization site and infrastructure to support the service,
- Providing the data standardization service for over 30 drug applications (INDs/NDAs), and
- Review and validation of test data sets provided by sponsors.

Significance: NIMS enables dynamic study visualization and analytics for the toxicology studies (currently general toxicology and carcinogenicity studies) as well as enabling cross-study metadata, and study data searching across the data repository. NIMS also allows for exporting to other tools for additional visualization or graphing as well as populating fields for the reviewer template.

FDA developed and provided scientific workstations to FDA staff.

Significance: Scientific Workstations offer alternative computing with more powerful CPUs and bigger CPU memories and disk spaces than the regular laptops FDA employees use. Reviewers can reserve time on these workstations to run programs and software that are too large or take too long to finish on individual laptops.

Through the Highly Integrated Virtual Environment, (HIVE), FDA developed the IT infrastructure to support data storage, transfer, and analytics that will allow it to review data based on next-generation sequencing (NGS). HIVE was used to help establish an analysis pipeline for next generation sequencing data that allowed virology reviewers to understand viral resistance data and carefully define resistance to antiviral drugs in the labels of Harvoni®, Olysio®, and Sovaldi®, three important drugs approved for combating hepatitis C virus. Virology reviewers in collaboration with HIVE programmers have designed new tools and modules to expedite the review of viral resistance data generated by next generation sequencing.

Significance: The HIVE platform and the new tools will allow reviewers to rapidly and efficiently assess terabytes of sequence information, and make better informed regulatory review decisions while operating within the confines of the regulatory review clock.

iii. Research Infrastructure

The continuing evolution of FDA's White Oak campus has created a vibrant scientific community that has increased cross-cutting opportunities for scientific collaboration and training. A newly completed South-East quadrant houses CBER, CTP, and additional CDER laboratory and review components. The Life Sciences Biodefense Laboratories represents a major investment in regulatory science infrastructure. Opened in summer, 2014, and housing some 100 research programs, this large new laboratory complex provides FDA with a state-of-the-art facility to support a number of advanced technologies. They include:

- New in vivo imaging capability (MRI, digital X-ray, etc.);
- In vitro imaging (high resolution confocal microscopy, TEM);
- A dedicated transgenic derivation facility,
- NGS technology (acquired by CDER internal lab (Division of Applied Regulatory Science)) for use in addressing review issues and assisting in the development/evaluation of standards and best practices for regulatory applications
- Expanded space to support NGS and associated bioinformatics/IT infrastructure (dedicated computer room)
- Multi-color flow cytometry;
- High resolution structural biology (mass spectrometry and NMR);
- Significantly expanded BSL-3 capacity, with a total of 10 BSL-3 suites, including a core BSL-3 suite for flow cytometry and confocal microscopy, BSL-3 insectarium, and several agent-specific BSL-3 suites with animal holding capacity;
- A BSL-2 insectarium for working with the causative agent of malaria; and
- Common space on each floor of the facility to house additional technology-specific needs, such as PCR rooms, microarray, and histology.

Significance: These investments in key novel technologies will support intramural regulatory science programs in order to prepare for regulatory evaluation of innovative medical products and to enhance evaluation tools available for existing products.

Department of Health and Human Services
Food and Drug Administration

This report was prepared by FDA's Office of the Chief Scientist in collaboration with the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), the Center for Devices and Radiological Health (CDRH), and the Office of Planning. For information on obtaining additional copies contact:

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