U.S. FOOD & DRUG ADMINISTRATION

FY 2015-2016:

Regulatory Science Progress Report

In Fulfillment of Requirements Under the

Food and Drug Administration Safety and Innovation Act, Section 1124

Table of Contents

Preface

This is the second of FDA's regulatory science progress reports in fulfillment of the requirement under Section 1124 of the Food and Drug Administration Safety and Innovation Act (FDASIA)[1] to report on progress made with respect to advancing the regulatory science priorities, resolving the scientific gaps, and reporting on the metrics that were outlined in the Strategy and Implementation Plan for Advancing Regulatory Science for Medical Products,[2] and to describe how advances in regulatory science were adopted and integrated across the FDA through guidance development and adoption of tools, methods and processes. The report is organized into the following five sections:

A. Advancing the science of medical product development and evaluation

B. Advancing product manufacturing and quality

C. Ensuring the safety and effectiveness of marketed medical products

D. Advancing regulatory science to promote global health

E. Infrastructure and organizational changes to advance regulatory science

FDA's intramural research program is broad in scope, and its research collaborations involve hundreds of partnering organizations. This report cannot describe every advance in regulatory science by the Agency and its impact. However, we provide many examples of areas where we have made significant impact. We also provide links to additional information for those seeking to understand how we have advanced regulatory science to contribute to the development of safe and effective medical products that advance public health.

FY 2015-2016 Regulatory Science Progress Report: Executive Summary

FDA is charged with determining and ensuring the safety, quality, and efficacy of medical products of increasing diversity and complexity. This responsibility shapes our scientific research portfolio, which seeks to develop the methods, tools, and standards needed to support evaluation of these products throughout their life cycle. Through guidance to industry, scientific publications, and open discussions at FDA-sponsored workshops and other forums, these methods, tools, and standards become valuable scientific resources in the public domain and furnish developers with clear pathways and expectations as they generate the evidence to support their products. FDA is also responsible for the oversight of manufacturing quality throughout the lifecycle of medical products. In addition, the Agency plays a critical role in protecting the United States from emerging public health threats. These additional regulatory responsibilities are also important drivers of our research agenda. To address them, in fiscal years 2015 and 2016, we made significant progress in the following areas:

Advancing the science of medical product development and evaluation

Refining non-clinical predictive models to support the evaluation of medical products:

FDA researchers developed and/or refined a wide variety of computational tools that now support nonclinical evaluation of medical products. These tools include sophisticated models to predict the carcinogenic effects of certain drug ingredients based on their structural attributes, mathematical representations of the human body (computational phantoms) that can be used to predict the effects of medical devices, such as exposure to radiation, and mechanistically informed pharmacokinetic models to help predict drug exposures in populations where clinical data are difficult to obtain. Genetic and transplantation approaches were used to create animal models that may more closely predict human response to medical products, and novel physical methods and procedures were developed to support

the evaluation of bioequivalence* of generic versions of locally acting drugs, like those acting in the skin or airways.

Improving clinical evaluation

To support clinical evaluation of medical products, our statisticians helped design trials of antibiotics that could evaluate factors related to development of resistant organisms. Through a carefully designed pathway to foster biomarker development and adoption†, we have qualified new biomarkers to guide treatment decisions and to predict disease progression. A long-term research effort to improve prediction of cardiovascular risks contributed to the recommendation by the International Conference on Harmonisation‡ that the costly and resource-intensive "thorough QT" clinical study (required to evaluate most drug candidates) could be replaced with electrocardiogram-based measurements performed during early-phase clinical studies.

Advancing product manufacturing and quality

Our medical product centers continued to address scientific issues related to new technologies critical for product manufacturing to improve the reliability of drug supply, characterization of complex products, quality standards, post-approval monitoring of product quality, and understanding of the complex interactions of regulated products with biological systems. We have developed in-house laboratory and computational capability for studying continuous manufacturing with an advanced process control system. We collaborated with the Biomedical Advanced Research and Development Authority[3] (BARDA) to leverage continuous manufacturing to minimize domestic vulnerability to chemical, biologic, and radiologic threats, and we spearheaded creation of a 3-D printing facility to understand factors contributing to the quality and performance of implantable medical devices, drugs, and combination products made with this new technology. We developed automated approaches for

*The term "bioequivalence" is defined under FDA regulations to include "[t]he absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives in the brand name and generic products becomes available at the site of drug action when administered at the same molar doses under similar conditions in an appropriately designed study. A drug product submitted for approval in an abbreviated new drug application (ANDA) is required to demonstrate bioequivalence to the listed drug it references. For a detailed definition of the term "bioequivalence," see 21 CFR § 320.1(e).

*This pathway is made available through the Biomarker Qualification Program: www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/default.htm Biomarker qualification is a conclusion, based on a formal regulatory process, that within the stated context of use, a biomarker can be relied upon to have a specific interpretation and application in drug development and regulatory review.

†The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) was established to allow FDA and its counterparts in the European Union and Japan to achieve greater harmonization in the regulation of medical products.

predicting critical properties of human stem cell preparations, such as their ability to contribute to bone growth.

Ensuring the safety and effectiveness of marketed medical products

Exceeding our commitments to develop a national electronic system for active medical product surveillance, we expanded the Sentinel[4*] system to include data from Medicare patients, and we developed new systems and tools for safety signal detection and interpretation. We worked with diverse stakeholders in the medical device ecosystem to further the development of a National Evaluation System for health Technology[5] (NEST) that will increase access to and use of real-world evidence to support regulatory decisions.

Advancing regulatory science to promote global health

The medical product centers supported the regulatory public health response to the threats of Ebola virus and Zika virus through development of tools, reference materials, and publication of science-based guidance to support rapid development of new medical products to diagnose, treat, or prevent diseases caused by these pathogens. Research efforts on other threats, such as pandemic influenza virus, continued to advance.

Infrastructure development and organizational changes to advance regulatory science

In the past two years, we enhanced information technology tools that support scientific review of regulatory applications. Following the success of the award-winning JumpStart service[6] that allows reviewers to organize, manage, and verify the quality of the clinical data in product applications, FDA initiated Kickstart, a service that delivers individual training and user-driven support and analysis for non-clinical data. To make possible the secure deposition, retrieval, and analysis of the vast next generation sequencing data that will support personalized medicine, we continued to enhance our high performance scientific computing environments. We extended our laboratory capabilities and facilities for mission-critical areas, including advanced manufacturing, analytical methodology, and emerging infectious diseases.

[*] Launched as part of FDA's implementation of the Food and Drug Administration Amendments Act of 2007 (FDAAA), Sentinel is the FDA's national electronic system for monitoring of the safety of FDA-regulated medical products.

Through organizational and programmatic changes, we have enhanced our ability to identify regulatory science issues and provide critical information for decision making. Within the Center for Drug Evaluation and Research (CDER), we created the Office of Pharmaceutical Quality to better align product quality research with review and inspection activities and established the Emerging Technology Program within the same office to support modernization of pharmaceutical manufacturing. Our Center for Biologics Evaluation and Research (CBER) established a regulatory science council to oversee research activities and revamped its peer review process. The Center for Devices and Radiological Health (CDRH) piloted a Regulatory Science Research Program Review to facilitate a feedback loop between CDRH reviewers and bench scientists. New programs to enhance scientific interactions with stakeholders, such as the Critical Path[7] Information meetings, saw a surge of interest from stakeholders.
The medical product centers also worked collaboratively to bring new efficiencies to research efforts by creating a unified program for animal research on the White Oak campus. A new shared resources program provided for multi-center funding and governance of large shared equipment and computing resources, [*] and our Challenge Grant programs continued to support innovative projects to advance regulatory science.

We shared our research with the medical product industry by publishing guidance documents[8] on many scientific topics—for example, how to formulate and validate reprocessing instructions for reusable medical devices, and how to evaluate abuse-deterrent properties of opioids. Our research contributed to the development of consensus standards providing medical product developers with clearer pathways to developing evidence for product approval. We sponsored public workshops to foster scientific exchanges[9] with stakeholders representing industry, government, the academic community, patient advocates, and the public. We conducted or participated in numerous training activities, professional and scientific meetings, and workshops to help our staff integrate new scientific knowledge into review and regulatory practice. We also expanded the number of our public-private partnerships to advance drug development, for example by inaugurating the International Neonatal Consortium,[10] whose purpose is to forge a predictable regulatory path for evaluating therapies for neonates.

[*] One of the first shared resources under this initiative was a 3-D printing facility, jointly funded and managed by the medical product centers, that will allow researchers to better understand the application of this technology to new products and to more effectively develop standards and guidance to facilitate product development.

The report "Regulatory Science Progress Report for FY 2015 and FY 2016" to fulfill the requirements under FDASIA Section 1124 [11] and summarize how FDA has advanced regulatory science to support medical product development in this time frame. The full report is available on the FDA website at www.fda.gov/RegulatoryInformation/Legislation/SignificantAmendmentstotheFDCAct/FDASIA/ucm356316.htm.

Introduction

FDA conducts a science program that is critical to supporting our regulatory and public health mission. The Agency's regulatory actions often receive more attention in the media than its scientific efforts, but its research portfolio is as diverse and critical to the Agency as its regulatory actions. Our research is driven by our regulatory responsibilities and the questions that arise during our review process. For example, is a particular laboratory assay appropriate for testing the biologic activity of an investigational drug? How reliable is a proposed imaging biomarker as an indicator of disease progression? Is a clinical trial to test the efficacy of the drug or device well designed and properly analyzed? If a product is proposed for a group of patients based on genetic criteria, are the methods used to determine their genotype reliable? Each new product or class of products raises new scientific questions that must be addressed to help ensure safety and efficacy.

Also, we must ensure that the products are produced in a way that maintains the highest quality standards. Therefore, FDA research encompasses cutting edge technologies like 3-D printing and systems to support continuous manufacturing with advanced process controls. Agency researchers investigate complex cell therapies used to treat cancer and other diseases, ensure that critical product quality attributes are maintained, and develop methods to make certain that products derived from biological sources are not contaminated with harmful microorganisms.

FDA is charged with collecting and analyzing information on medical products to ensure they are safe and effective as used by the public. We must therefore develop sound statistical methods and computational approaches to interpret the vast and complex data from clinical trials, as well as the adverse events that may occur when drugs, biologics, devices, and combination products are used in real-world settings.

FDA's regulatory responsibility to evaluate medical products drives our research agenda, but the outcomes of this research also directly foster and stimulate new medical product development. At each step of product development, a sponsor seeks to measure important product attributes predictive of final performance and quality. Therefore, the availability of sound analytical frameworks and reliable methods is integral to the success of each medical product's development process. Similarly, FDA's effective regulatory evaluation and oversight relies on robust measures of product performance and quality. Developing innovative methods and analytical approaches to assess product attributes and performance is a common goal of all stakeholders, but FDA scientists, by virtue of their access to and understanding of information contained in a wide range of medical product development programs, bring a unique perspective to these efforts. They can identify important principles, best practices, and methods for successful development that apply to a wide range of medical products. FDA's scientific efforts focus on making available methods and tools that can promote the success of development programs. To ensure that FDA's findings and descriptions of new methods and models to support product development are communicated to all stakeholders, they are described in peer-reviewed scientific journals, discussed at public workshops, integrated into guidance to industry, and incorporated into internal and external training programs. FDA also hosts individual meetings to develop specific

products or drug development tools. This report will highlight certain FDA guidances that enable clear communication to product developers based on the best available scientific knowledge and insights.

A. Advancing the Science of Medical Product Development and Evaluation

Each year FDA receives thousands of regulatory submissions for new and generic drugs, biological products, including biosimilar biological products, medical devices, and combination products. The increasing diversity, complexity, and technologic sophistication of these products drives a research portfolio focused on developing methods, tools, technologies, and statistical and analytical frameworks sufficient to evaluate these unique medical products and ensure their safety and efficacy. Here, we describe some recent accomplishments and provide additional sources of information about research advances that support the evaluation of medical products.

1. Developing Modeling and Simulation Approaches to Evaluate Medical Products

Computational modeling[*] and simulation play an expanding role in the evaluation of medical products throughout their lifecycle and are increasingly used by developers. There are several reasons for this trend: *In silico* experiments made possible by the rapid advances in scientific computing can save costs, for instance by allowing for rapid early screening of candidate molecules and reducing the need for costly animal studies. In some cases clinical testing, for example to determine the radiation exposure caused by a medical device, would be unethical. And computational approaches also allow investigators to quickly test products under various conditions of use and for diverse groups of patients—testing under a comparable diversity of conditions would often not be achievable using laboratory-based approaches alone.

a. FDA researchers have developed new computational tools and approaches for preclinical drug evaluation and made them available to the product development community

As described in the Strategy and Implementation Plan for Advancing Regulatory Science for Medical Products[12] published in 2012, new and improved toxicology models are essential tools that provide relevant safety information for medical products. One of the most important classes of models for providing this information are quantitative structure-activity relationship (QSAR)[†] models, in which a

[*] Modeling is the development of a mathematical representation (model) of an entity, system or process. Simulation refers to the procedure of solving on a computer the mathematical equations that resulted from model development.

[†] FDA researchers generate two kinds of structure-activity relationship models. QSAR (quantitative structure-activity relationship) models are usually generated through machine-learning and are in the form of a mathematical equation. SAR (structure activity relationship) models describe qualitative relationships between the absence or presence of molecular features and toxicity or other properties. The acronym QSAR refers to both kinds of models.

collection of molecules with known toxicities are used to derive a mathematical relationship between a drug's structural attributes and whether it will cause a certain biological effect (e.g., a certain toxicity). Over the past two years, FDA researchers and collaborators in private industry have developed additional and more sophisticated QSAR models to evaluate drug products. In 2015, FDA, along with international regulatory agencies, decided that QSAR models can be used to predict the mutagenicity* of impurities found in drug products in place of traditional and more costly experimental approaches. That same year, FDA published a guidance[13] describing in detail how the models should be used. QSAR models are also valuable for screening candidate drug molecules for unwanted toxicities before conducting further testing in animals.

- ✓ FDA researchers and collaborators developed 10 new QSAR models and made them available to the drug development community. These models can be used to help determine which candidate drug molecules to move to the next stage of testing or whether certain chemicals in their products are likely to be carcinogenic.
- ✓ FDA's Adverse Event Reporting System (FAERS)[14] is a rich source of information about the potential side effects of drugs. FDA researchers have recently developed computational methods that can be used to classify organ-specific toxicities collected in FAERS. This work can provide new modeling data from which to build new QSAR models relevant to various disease areas. Learn more.[15]
- ✓ In 2015 and 2016, FDA/CDER's QSAR Computational Toxicology Consultation Service[16] provided extensive QSAR analyses and structural similarity-based assessments to CDER safety reviewers. These consults help reviewers resolve inadequate or equivocal experimental results and understand unanticipated post-market safety signals.

b. FDA researchers developed computational modeling and simulation methods and tools to evaluate medical devices

Modeling and simulation methods also play an increasing role in the development and evaluation of medical devices (for example, stents, orthopedic implants, intraocular lenses, and heart valves) submitted to FDA. The Agency recently developed new computational tools and resources that can assist developers when using modeling approaches to evaluate devices. These include highly sophisticated computational models of patients (e.g., the Virtual Population[17] and Multimodal Imaging-Based Detailed Anatomical Model of the Human Head and Neck (MIDA)[18] that can be used to simulate the effects of radiation from medical devices.

In the area of medical imaging, FDA scientists have pioneered computation and modeling approaches for analyzing and evaluating magnetic resonance imaging (MRI)[19] and computed tomography (CT),[20] including digital breast tomosynthesis.[21] In the course of its research, FDA is developing capabilities to simulate all aspects of the imaging process (for example, the radiation emitted, its interaction with the patient, the detection of the radiation, image reconstruction, and the interpretation of the image by

*A substance is mutagenic if it causes genetic changes.

medical personnel). In principle, computational tools can be combined into a seamless approach to support the evaluation of imaging technologies. To that end, FDA recently initiated the Virtual Imaging Clinical Trials for Regulatory Evaluation[22] (VICTRE), a project that seeks to make an all-digital imaging pipeline available for simulating three-dimensional (3-D) breast imaging systems that are now approved based on burdensome clinical trials. One goal of FDA researchers is to demonstrate that virtual clinical trials to evaluate emerging medical imaging technologies can, in some cases, supplant or significantly minimize the need for studies that require patients to be exposed to radiation.

Modeling and simulation approaches developed by FDA researchers have been used to evaluate other product types. Computational models of transcatheter heart valves[23] used in the treatment of aortic stenosis supported recommendations by the International Organization for Standardization[24] (ISO) for preclinical testing of the longevity and durability of these devices. In addition, a model of drug release into vascular tissue[25] that takes into account variations in tissue structure provided a framework to assess drug release to specific locations (deposition) of drug-eluting technologies, such as the drug-releasing stents used to treat atherosclerosis.

Resources made available by FDA to researchers and developers that advance computation and simulation approaches include the following:

- ✓ The Virtual Population[26] Created as a joint effort by FDA and the IT'IS Foundation,[27] the Virtual Population is a set of highly detailed, anatomically correct, whole-body computational models that were developed based on high-resolution magnetic resonance imaging (MRI) data. They are used to assess energy exposure and medical device safety (e.g., pacemakers, spinal cord stimulators, and orthopedic implants) in patients undergoing MRI. Because a single MRI procedure in a hospital costs an average of $2,500, these models can support tremendous savings to developers and bring products to the market faster. New releases of the models in 2015 allow for the virtual patient to assume various postural changes. The Virtual Family/Population models have been used by over 400 research groups, and were used in 16 medical device regulatory submissions to FDA in FY 2015.

- ✓ MIDA - A Multimodal Imaging-Based Model of the Human Head and Neck[28] In 2015, FDA and partners developed a multimodal imaging-based detailed anatomical computer model of the human head and neck that greatly advances our ability to simulate electromagnetic effects on patients from medical devices. The MIDA model has been used by FDA researchers to map the electrical fields caused by deep brain stimulators[29] used in the treatment of Parkinson's disease and to evaluate devices that induce transcranial alternating current[30] (a potential treatment for cancer and other diseases).

- ✓ Evaluation Environment for Digital and Analog Pathology (eeDAP).[31] The evaluation of digitized information (digital pathology) from pathology slides is considered one of the most promising avenues of diagnostic medicine for achieving more accurate, efficient diagnosis, prognosis and prediction of cancers and other diseases. However, comparing findings based on digital pathology with those based on optical microscopy can be difficult. FDA and partners developed eeDAP to design and execute pathology studies where evaluation of regions of interest in the digital image is registered to the real-time view on the microscope. This registration allows for the reduction or elimination of a large source of variability in comparing digital pathology to traditional approaches. The new platform will allow for the validation of

whole-slide imaging systems relative to optical microscopy approaches so that their advantages (e.g., for purposes of telepathology and digital consultations) can be realized in health care settings. Learn more.[32]

- Additional computational resources developed by FDA and collaborators for use by the product development community[33]
- Learn more about recent research by FDA scientists that developed methods for the evaluation of medical devices using modeling and simulation approaches[34] (under "Research by Special Topics," see computational modeling and software)
- Recent guidance issued by FDA on medical device evaluation using computational approaches[35]

2. New Laboratory Methods and Tools for the Preclinical Evaluation of Medical Products

FDA develops methods, technologies and systems to support the development and evaluation of the next generation of medical products.[*] The number and diversity of the products evaluated and the questions addressed by FDA laboratories is such that we cannot fully summarize the research accomplishments in this report. We highlight some new methodologies for evaluation of drugs and biologics, including generic drugs not delivered through the systemic circulation. We also describe some new tools for the evaluation of medical devices, and provide comprehensive sources of information.

a. FDA researchers are developing evaluation methods that support development of generic drugs, biosimilars[†], and protein therapeutics

Among other requirements, in an application to market a generic drug, an applicant must demonstrate that its product is pharmaceutically equivalent[‡] and bioequivalent to a reference listed drug.[§] Diverse laboratory methods may be used to demonstrate pharmaceutical equivalence, and often, traditional bioequivalence studies are performed by measuring the drug's concentrations in the blood over a specified time period. FDA publishes product-specific guidances that assist developers with identifying

[*] For example, research at FDA's Office of Science and Engineering Laboratories to develop methods to analyze the effects of MRI on pacemakers, was a critical step in the development of pacemakers that were compatible with MRI exams.

[†] Section 351(i) of the Public Health Services Act defines the term "biosimilarity" to mean that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components," and "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." (For further discussion about biosimilar products, See FDA guidance for industry *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*, available on the FDA's Web page at *www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291128.pdf*).

[‡] Drug products are considered "pharmaceutical equivalents" if they contain the same active ingredient(s), are of the same dosage form, route of administration, and are formulated to contain the same amount of active ingredient, and to meet the same or compendial or other applicable standards (i.e., strength, quality, purity, and identity) identical in strength or concentration. The term "pharmaceutical equivalents" is specifically defined by FDA regulations at 21 CFR § 320.1(c).

[§] See FDA draft guidance for industry *Referencing Approved Drug Products in ANDA Submissions*, available on the FDA's Web page at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536962.pdf.

the most appropriate methodology to generate evidence needed to support approval of a generic drug application.[*]

- ✓ In FY 2015 and 2016, FDA published over 248 new product-specific guidances for generic drug products and made revisions to an additional 110 such guidances.

For many classes of products whose route of delivery is not primarily through the bloodstream (e.g. products topically applied to the skin, ophthalmic products, and orally inhaled and nasal products), establishing bioequivalence can present a scientific challenge. For these products, FDA research has provided developers with new approaches for establishing bioequivalence. They consist of a collection of carefully evaluated in vitro methods often coupled with modeling approaches.

- ✓ FDA has developed and/or refined advanced in vitro/in silico methods such as computational fluid dynamic modeling and clinically relevant in vitro dissolution and deposition tests. These tests and methods will help us to understand and better predict performance of orally inhaled and nasal products and may allow for fewer burdensome clinical endpoint bioequivalence studies. Learn more.[36]

- ✓ FDA research has resulted in the validation and availability of a significant new methodology for establishing the bioequivalence of generic drugs applied to the skin called small dermal open flow microperfusion. The method allows for sampling of local concentrations of a drug in the skin of humans, thus monitoring the rate and extent to which a topically administered drug becomes available at the site of action. Learn more.[37]

- ✓ Through research on in vitro characterization, drug release, and modeling of drug delivery, FDA has developed methodologies for establishing bioequivalence of ophthalmic products. Outcomes of this research include guidances on a characterization-based bioequivalence approach for Cyclosporine and Difluprednate[38] emulsions, and product-specific guidances for ten ophthalmic suspensions.

- ✓ Glatiramer acetate (Capoxone), used to treat relapsing forms of multiple sclerosis, is a mixture of small protein fragments, and it is unknown exactly which components of the mixture are important for therapeutic activity. FDA scientists developed sensitive analytical approaches coupled with advanced statistical methods to characterize and differentiate among slightly different mixtures. These methods will help ensure that glatiramer acetate products are of high quality. The first generic glatiramer acetate product was approved in 2015. Learn more.[39]

- ✓ There are also other recent product-specific guidances that provide developers with pathways for generic drug development.[40]

- ✓ Learn more about recent FDA research to promote generic drug development–Office of Generic Drugs FY 2015 Regulatory Science Report.[41]

[*] FDA regulations outline the types of evidence that may be used to establish bioequivalence. See 21 CFR § 320.24. See also, FDA's draft guidance for industry Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA, available on the FDA's Webpage at www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM377465.pdf.

FDA researchers also developed methods that will foster the development and evaluation of protein therapeutics and biosimilars.

- ✓ In collaboration with the National Center for Biotechnology Information, FDA developed two tools: 1) HA Predictor, which predicts the outcome of mutations in recombinant factor 8 and factor 9 genes*, and 2) RemuRNA, which predicts RNA conformation and stability. These tools will assist in the development and evaluation of genetically engineered protein therapeutics. Learn more.[42]

- ✓ FDA researchers investigated the suitability of a spectroscopic method called two-dimensional nuclear magnetic resonance (2D-NMR) and found that it could capture complex structural information on a protein with high precision. Because this method allows for the detection of small local differences throughout complex structures, it will have broad applicability in evaluating biosimilarity and product quality for a number of products that are revolutionizing medicine. Learn more.[43]

b. FDA has developed in vitro methods and tools that help us understand the properties of drugs, biologics, including vaccines

Among recent research advances were the following:

- ✓ Using stem cells that are induced to form heart muscle cells, FDA researchers have advanced development of in vitro approaches to reproduce and analyze clinically observed effects of various drugs on heart function. The responses of these cells to various drugs are assessed using microelectrode arrays or voltage-sensitive dyes and optical imaging. Development of these in vitro technologies, a key component of the CiPA Initiative,[44] has the potential to improve prediction of the effect of drugs on the heart.

- ✓ The complexity of multipotent stem cells (MSCs), raises unique challenges in a regulatory setting. Characterizing MSC-based products is complex because of several reasons including the following: heterogeneity among donors as well as within a population of cells from a given donor, the cells' ability to differentiate into new functional phenotypes, and the potential risk of transforming into a tumorigenic phenotype. To address these regulatory science needs, FDA researchers have been investigating human MSCs (hMSCs) to identify product quality attributes that correlate with measurable functional outcomes. They have applied a variety of tools and developed new methods to assess gene expression at the RNA, microRNA, and proteomic levels, as well as the chromosomal stability and epigenetic status of hMSCs. This work has resulted in new in vitro assays, and other technologies to evaluate how to predict quality, potency, and safety of these complex cell-based products.[45]

- ✓ In vitro immune assays were used to understand how certain antibodies in infected individuals interfere with antibodies that block hepatitis C infection. The findings will augment efforts to develop improved intravenous immunoglobulin-based products to treat the viruses and develop effective vaccines. Learn more.[46]

* These genes encode Factor VIII and IX, and defects in them cause hemophilia.

- ✓ The human lymphocyte transformation test (LTT) has been used for decades to test for metal-associated allergic reactions, but the predictive value of the test is still controversial. The method requires labeling with radioactive isotopes and gives no information on cell viability or corresponding lymphocyte subsets. FDA researchers developed an alternative test that can differentiate responses of specific kinds of immune cells without the use of any radioactive isotope labeling. Because the test removes radioactive isotope exposure and is safer and more accurate than the traditional LTT, results can specifically address an individual's risk.

c. FDA engineers and physicists are developing the tools needed to evaluate medical devices

The diversity of medical devices regulated by FDA means that the scientific research supporting their evaluation spans many disciplines. For a summary of research supporting the evaluation of new medical devices, see the website of the FDA Center for Devices and Radiological Health, which summarizes recent research progress across clinical areas and special topics.* Here, we present examples of recent scientific advances by FDA researchers that support evaluation and development of medical imaging technologies.

- ✓ Optical coherence tomography (OCT) is used to monitor for glaucoma and its progression by measuring dimensions of the optic nerve. FDA researchers constructed three phantoms† and used them to assess the measurement characteristics of different OCT devices. This research highlighted significant differences among devices in clinical use and suggested that phantoms could help achieve standardized results in glaucoma diagnosis across different platforms. Learn more.[47]

- ✓ Endoscopy is an imaging procedure with wide medical applications, including the diagnosis and treatment of diseases of the digestive tract. FDA researchers tested two algorithms for the correction of geometric distortion caused by lens effects in endoscopy. This research will contribute to development of standardized test methods for characterizing distortion and other optical performance characteristics of these devices. It will facilitate development of endoscopic technologies, and improve their manufacturing quality and performance during clinical use. Learn more.[48]

- ✓ Using physical phantoms containing synthetic nodules that closely resembled actual lesions in lung cancer, FDA researchers compared different image acquisition and reconstruction parameters for computed tomography. These studies enhanced our understanding of the sources of biases that could occur in the clinical setting. Learn more.[49]

- ✓ Although high-field magnetic resonance imaging (MRI) has advantages over new low-field methods, it can raise safety concerns due to the amount of radiation absorbed by the patient. FDA researchers developed a novel method to decrease the energy absorbed by the patient and tested it using physical measurement

* For about 30 research areas, one can find information on recent research accomplishments and guidances and consensus standards to which the research has contributed. www.fda.gov/MedicalDevices/ScienceandResearch/ResearchPrograms/default.htm.

† A phantom is a specially designed object that is scanned or imaged in the field of medical imaging to evaluate, analyze, and tune the performance of the imaging device.

simulations. The new approach to decreasing electric field and patient exposure can be incorporated into the design of radiofrequency coils in MRI devices. Learn more.[50]

d. Improving animal models for the evaluation of medical products

Animal studies play a critical role in preclinical testing of the safety and effectiveness of medical products, and may be important for understanding the reasons for adverse events in marketed products and devising strategies to prevent them. However, developing an animal model that predicts human response can be challenging. Genetic and transplantation methods can be used to modify an organism so that it more closely mimics human biology or a specific disease condition. Well-characterized biomarkers and advanced imaging techniques applied to the animal model can help investigators to adequately monitor complex responses related to the safety and efficacy of the product.

To address questions related to review of medical products, FDA researchers have developed and/or refined a wide variety of animal models that more closely resemble humans in their responses to drugs, biologics, and vaccines and can serve as valuable scientific resources to the medical product development community.

- ✓ FDA researchers used a mouse with a humanized immune system to isolate human mast cells (these cells are embedded in tissue and cannot be obtained from human donors). This allowed them to confirm the identity of an additive to an erythropoietin* analog that had caused severe adverse reactions. The mouse model is currently being applied to the evaluation of cancer therapeutics to treat leukemia. Learn more.[51]

- ✓ Blood-derived immunoglobulins are used to treat various disorders. Immunoglobulin G [IgG] can cross the placenta and may pose a threat to the fetus when given to pregnant women. Previous research partially clarified the mechanism by which this passage occurs, but more information is needed to develop techniques for evaluating this mechanism using both animal models and in vitro studies, such as those using cell cultures. Using female guinea pigs whose stages of pregnancy could be tracked, FDA researchers were able to measure the increasing fetal:maternal ratio of IgG from about day 26 to day 54 of gestation. This model will assist in the development of appropriate laboratory systems for assessing the risks associated with transport of IgG-based therapies across the placenta. Learn more.[52]

- ✓ Using a baboon model, FDA researchers found that the whole cell versions of a vaccine against diphtheria, tetanus, and pertussis accelerated the clearance of *B. pertussis* following challenge compared with an acellular form of the vaccine, which had been introduced due to concerns about fever and other side effects. FDA researchers found that, in baboons, a specific gene (IL-17) involved in cell-mediated immune response, was increased when exposed to the whole cell version of the vaccine but not the acellular version. This suggested a strategy (using adjuvants to increase IL-17 expression) to boost responses to acellular vaccines. Learn more.[53]

* A hormone that stimulates production of red blood cells.

- ✓ Antibodies against major influenza epitopes in the HA and NA genes (these genes encode hemagglutinin and neuraminidase, proteins on the surface of flu virus) were evaluated in mice to elucidate immune responses against H7N9 and H1N1 strains of influenza. Antibodies generated to the hemagglutinin epitope of H7N9 influenza virus were able to provide protection against H7N9 challenge and were cross reactive to some H7 strains. Learn more.[54] An additional study compared effectiveness of antibodies to H1N1 and H5N1 neuraminidase epitopes. Learn more.[55] Results from both studies help us understand the roles of specific antibodies in influenza immunity.

- ✓ Respiratory Syncytial virus (RSV) is one of the leading causes of pneumonia among infants. In a vaccine animal model, mice were immunized with two variants of an RSV vaccine to examine the role of glycosylation. Researchers found that the non-glycosylated vaccine is protective and does not initiate disease enhancement as seen with the glycosylated vaccine. Insights gained from this study will assist in the development of protective and safe vaccines against RSV. Learn more.[56]

- ✓ FDA scientists tested a candidate universal influenza vaccine (i.e., one that protects against a broad spectrum of influenza viruses) in mice of different ages, both for immune responses and protection against challenge infection. The findings suggest there may be advantages (in terms of protection later in life) to vaccinating individuals when their immune system is young and optimally responsive, and that the vaccine may be useful for the elderly if given with an enhanced regimen. Learn more.[57]

- ✓ Gene therapies are often delivered via vectors derived from viruses, and these vectors have complex interactions with the body that influence gene delivery to targets of interest. Using a mouse model, FDA researchers investigated the mechanisms associated with poor efficacy outcomes for certain types of gene therapy products. Findings from these studies will enable development of new therapies that can reach various therapeutic targets (for example, liver cells to treat inherited diseases like hemophilias). Learn more.[58]

3. Improving Clinical Evaluation of Medical Products

FDA is engaged in wide-ranging efforts to make clinical trials more sound, informative and efficient. Clinical pharmacologists are helping sponsors design early-phase clinical trials to determine the safest and most effective doses of candidate drugs and biologics, and also developing methods for predicting drug exposures based on available clinical and nonclinical data in the many patient groups that may not be represented in a trial. Statisticians are addressing fundamental questions pertaining to trial design and analysis. The Agency is engaged in wide-ranging efforts to advance the development and evaluation of biomarkers that can be used to predict long-term treatment outcomes (and thus streamline clinical trials) or to assign certain patients to treatments more likely to succeed. FDA and its partners are developing data standards and clinical trial databases to ensure that clinical trial data can be used to the fullest extent possible in medical research and regulatory decision making. The Agency has also been advancing clinical evaluation of medical products in settings outside of traditional clinical trials, leading scientific initiatives to utilize all available sources of relevant data to inform the safe use of medical products and to make medical products and information available more quickly to the public.[59]

a. Clinical pharmacology research in support of drug development and review

The discipline of clinical pharmacology[60] comes into play at multiple stages of drug development and review: after preclinical testing, a candidate drug may move to the early phase of clinical development with the submission of an investigational new drug (IND) application. FDA clinical pharmacologists review these applications and help to determine if the dose of the drug proposed to be used in the initial clinical studies is appropriate. If drug testing proceeds to phase 2 and phase 3 trials, they help determine dosing and design elements. And If a drug is to be approved based on positive results in phase III, drug labeling (stating at which dose, in which patients, and under what conditions the drug may be used) must be developed. Clinical pharmacology is also critical to evaluating many generic products, because for these products, the crucial question may be the similarity of drug exposure between the generic and the comparator product, its reference listed drug.

Clinical pharmacology research at FDA provides the drug development community with a variety of resources that inform and enhance clinical studies of drug products and accelerate drug development:

- ✓ In 2015, FDA developed a publicly available database[61] of quantitative information on drug-drug interactions and kidney and liver impairment stemming from drug exposure. This resource is meant to assist the drug development community in arriving at recommendations for evaluating drug exposures in patients with organ impairment or those receiving concomitant medications.

- ✓ FDA scientists helped to develop guidelines for reporting results of genetic tests in clinical pharmacology studies.[62] These guidelines will facilitate the adoption of clinical pharmacogenetics testing.

FDA's clinical pharmacologists continually review submissions to the FDA to identify ways to facilitate drug development.

- ✓ In 2015, FDA researchers analyzed 44 failed clinical trials for drug products in children[63] to identify factors associated with failure, and made recommendations for improving such trials.

- ✓ FDA researchers examined data from clinical trials and drug reviews to determine how chronic kidney disease may affect the elimination of drugs from the body.[64] This will help drug developers determine which drugs can be safely used in patients with chronic kidney disease.

As they review drug applications, FDA researchers develop exposure-response[65] or physiologically based pharmacokinetic models[66] that can allow for extrapolation of results to patient populations not studied in the clinical trials that supported drug approval.

- ✓ In a collaborative Critical Path research project entitled the Pediatric Epilepsy Academic Consortium for Extrapolation (PEACE) Initiative,[67] FDA researchers conducted exposure-response analyses based on available clinical data. They concluded that efficacy results in adults could be applied to children 4 years of age and older with partial onset seizures, and therefore, independent clinical efficacy trials in these children would not be needed. This conclusion will allow children to have better access to these needed drugs.

b. Improving clinical trials

Clinical trials are a complex undertaking, but they are essential for assessing the safety and efficacy of FDA-regulated medical products. Those seeking to evaluate new medical products must address the problem of missing data that can occur due to patient attrition, the length of time it may take to measure treatment outcomes (for example, in chronic diseases and certain cancers), and heterogeneity among patients. Moreover, it can be difficult to enroll sufficient numbers of patients in a given subgroup for reliable comparisons. These and many other issues make the design and conduct of clinical trials one of the most challenging aspects of medical product development.

FDA statisticians are developing novel approaches to make clinical trials more efficient and informative. Recent research has focused on the problem of incomplete data, such as incomplete data due to dropout in efficacy trials,[68] statistically sound methods for testing multiple hypotheses in the context of a single trial,[69] new approaches to noninferiority trials,[*] and the design of adaptive clinical trials.

- ✓ Trial designs developed by FDA researchers and collaborators included a new approach for assessing new antibiotics[70] that takes into account the duration of antibiotic use.
- ✓ FDA has described objective study design approaches, as well as analytic methods, for the conduct of clinical trials involving medical devices that leverage real world evidence, such as registries, or previous trial data.
- ✓ FDA has developed methods to analyze data from clinical validation studies for companion diagnostic assays that are used to determine whether a drug or biologic is applicable to an individual patient.
- ✓ FDA statisticians modified a minimization method[71] in a manner that leads to more accurate assessments of a statistical test used to evaluate products in small trials sizes (such as rare disease populations), while still balancing for variation in subjects at baseline.
- ✓ FDA has supported the adoption of innovation in clinical trials designed by the product development community. The Agency has published whitepapers and reviews of clinical trials that are contained in certain regulatory submissions. FDA has also produced tutorials on issues in trial analysis, and guidance for industry on adaptive designs for clinical studies of medical devices[72] and non-inferiority trials.[73]
- ✓ FDA scientists conducted a six-year retrospective survey that gathered information on the submission and evaluation of adaptive design proposals from product sponsors. Results from the survey were published to provide recommendations for developing such proposals for clinical trials in order to encourage the best study design proposals. Learn more.[74]

[*] Noninferiority trials test whether an experimental treatment is not materially worse than an active control. For further discussion about non-inferiority trials, see FDA's guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness*, available at www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm202140.pdf.

- ✓ FDA researchers are playing a leading role in revising international guidelines for the design, conduct, safety, and reporting of clinical trials, including ICH E9 Statistical Principles of Clinical trials,[75] and ICH E17,[76] which provides general principles for the planning and design of multiregional trials.

- ✓ FDA has pursued more efficient and data-driven approaches to quality oversight of clinical trials. It has recently embarked on a Cooperative Research and Development Agreement[77] (CRADA) with CluePoints to develop and test software that may indicate problems with clinical trial quality. The software will inform site inspection processes and the efforts of clinical and statistical reviewers to effectively and efficiently analyze clinical trial data.

c. FDA researchers and collaborators have fostered biomarker development and evaluation

Biomarkers are characteristics that are objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or biological responses to a therapeutic intervention. These instruments are critical to improving evaluation of medical products in clinical trials. For example, they may be used to assign patients to subgroups that are more likely to respond positively to a treatment, or in the context of a clinical trial, they may be used to predict long-term outcomes, like survival. Multiple biomarkers[78] have been accepted and used as outcome measures in clinical trials, and have been the basis for drug and biologic approvals. Through a variety of research efforts, regulatory mechanisms and research collaborations, FDA has sought to further the integration of these tools into medical product development.

- ✓ Recognizing that confusion about definitions and inconsistent use of key terms was impeding progress in biomarker development, an FDA-NIH Biomarker Working Group published the BEST[79] (Biomarker, Endpoints and other Tools) glossary[80] in 2016. It includes a glossary of terms and definitions that will ensure the consistency and clarity needed to drive progress in biomedical research and clinical care.

- ✓ FDA convened a scientific workshop[81] that brought together leaders from government, academic, industry, and patient advocacy groups to identify challenges and strategies to advance biomarker development.

- ✓ Working closely with the Quantitative Imaging Biomarker Alliance[82] (QIBA), FDA researchers have developed a general framework for evaluating the technical performance of quantitative imaging tools to support the development and evaluation of robust imaging biomarkers.

- ✓ In 2015-16, FDA qualified three new biomarkers for use in clinical trials through the Biomarker Qualification Program: galactomannan for enrollment in, and analysis of, clinical trials conducted to evaluate the efficacy and safety of drugs for the treatment of Invasive Aspergillosis,[83] fibrinogen as a prognostic biomarker for enrichment of clinical trials in Chronic Obstructive Pulmonary Disease,[84] and total kidney volume as a prognostic imaging biomarker for enrichment of clinical trials in Autosomal Dominant Polycystic Kidney Disease.[85] All three were qualified to aid in patient selection for clinical trials.

- ✓ Duchenne muscular dystrophy (DMD) is a relentlessly progressive and fatal genetic disease for which there is no cure. It is caused by mutations in a gene that produces the protein dystrophin. Drugs that can increase levels of functional dystrophin have been a recent focus of development. To create a pathway to approve new drugs for muscular dystrophies based on dystrophin expression as a biomarker, FDA researchers systematically analyzed the antibody methods used to detect the protein, and evaluated

scientific and regulatory considerations related to the use and interpretation of biomarker levels in clinical development plans. Their work has resulted in a guidance to industry[86] that clarified clinical development programs and trial designs for drugs to treat muscular dystrophy.

- ✓ FDA researchers have made advances in developing biomarkers for early detection of traumatic brain injury,[87] which will support the development of new therapeutics, and aid clinical management of this condition.*

- ✓ Torsades de Pointes (TdP), is a potentially fatal abnormal heart rhythm. After it was found that diverse drugs in many therapeutic categories could cause TdP, FDA and other worldwide regulatory agencies began to require a standalone clinical study called a Thorough QT (TQT) Study to ensure that drugs under development did not present a risk for TdP. However, these studies are costly and time consuming: since 2006, approximately 450 TQT studies have been performed at a cost to drug developers of over a billion dollars. FDA researchers evaluated a new approach[88] in which a drug's effect can be reliably assessed based on data from the small clinical studies that are routinely conducted to first test a new drug's safety in humans. They found that drug effects as measured using their new approach were in close agreement with those from previous TQT studies. This work paved the way for the December 2015 release of an updated ICH E14 Q & A,[89] which supports this important cost-saving alternative pathway to assessing the cardiac safety of new drugs.

d. FDA has developed instruments for clinical evaluations that are based on the patient perspective

Through initiatives such as the Patient-Focused Drug Development Initiative[90] (PFDD), the Patient Engagement Advisory Committee, and the Patient Preference Initiative, FDA is incorporating the patient viewpoint into medical product development and evaluation, and is seeking to understand the factors that are most important to patients (for example, disease symptoms that have the most impact and what would constitute an ideal treatment). Fulfilling commitments under the fifth reauthorization of the Prescription Drug User Fee act, FDA convened 10 PFDD meetings in 2015 and 2016, developing "Voice of the Patient Reports" for each. These meetings are helping the Agency to develop clinical outcome assessments (COAs)† through the Drug development Tools (DDT) Qualification Program. FDA recently made available a Clinical Outcome Assessment Compendium[91] that describes how certain clinical outcome assessments have been used in clinical trials to measure patient experience, identifies clinical outcome assessments that have been qualified for potential use under the DDT Program, and recognizes ongoing qualification projects to encourage community collaboration in the development of COAs for unmet needs.

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* A public workshop on this topic was convened in March 2016.
www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm483551.htm

† Clinical outcome assessments (COAs) measure a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions, and may be used to determine whether or not a drug has been demonstrated to provide a clinical benefit.
www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm

- ✓ COAs submitted/qualified through Clinical Outcome assessment qualification program[92]

- ✓ FDA led a pioneering study that demonstrated an approach to incorporating patient preference information into regulatory decision making. A large, representative sample of patients was surveyed about medical device risks they were willing to accept in exchange for weight loss. This data was considered during the 2015 approval of a novel weight loss device,[93] the first FDA-approved device to address obesity since 2007. The quantitative patient preference information from the study has since been used to design clinical trials for other new weight loss devices. Following this proof-of-principle study, FDA published guidance on the voluntary submission of patient preference information with marketing applications for medical devices.[94] FDA also collaborated with the Medical Device Innovation Consortium, a public-private partnership between industry, patient groups, and government agencies, to create a framework report on patient-centered benefit-risk assessment.[95] The report includes a catalog of methods that may be used to assess patient preferences in a way that generates valid scientific evidence to inform regulatory decision making.

B. Advancing Product Manufacturing and Quality

The 2013 Strategy and Implementation Plan for Advancing Regulatory Science for Medical Products[96] stated that "application of novel science and technologies is leading to new methods of manufacturing and to innovative products that are often complex" and that "efforts to promote the adoption of state-of-the-art manufacturing strategies . . . must continue." It stipulated the need for advanced analytic technologies to characterize increasingly complex products and measuring critical product quality attributes. Major FDA research efforts in FY 2015 and FY 2016 focused on advancing new emerging technologies to support manufacturing science, improving quality standards in critical areas (e.g., abuse-deterrent opioid products), and developing methods and tools to better characterize complex biologic products. Based in part on this research, FDA published several guidances to support manufacturing science and product quality that provided clearer pathways for product development and approval. Approved products included the first four biosimilar drugs, dozens of devices that were produced using 3-D printing, the first 3-D printed drug, and the first drug produced with continuous manufacturing.

1. Advancing Additive Manufacturing (3-D Printing) of Medical Products

Additive manufacturing (the term is often used interchangeably with 3-D printing) is the process of joining materials to make objects from 3-D model data, usually layer upon layer, as opposed to successively cutting material away from a solid block of material. This approach allows for fabrication of devices that were previously impossible to create and it has the potential to advance precision medicine by enabling fabrication of patient-specific drugs and devices, including drug dosage forms that might otherwise be unavailable. It is increasingly used to make products that FDA oversees.

- ✓ Based on data from a public workshop[97] in October of 2014 at which stakeholders provided input on the technical challenges associated with the use of additive manufacturing, FDA released a guidance[98] that outlined technical considerations associated with additive manufacturing processes. The guidance also provided recommendations for testing and characterization for devices made by 3-D printing.

- ✓ Because of their complex structures, the cleaning of devices produced by additive manufacturing is an area for research and test standards development. FDA scientists conducted studies to investigate the design and build conditions for cleaning these devices. These studies underscored the need for updated standards in this area.

- ✓ FDA established an additive manufacturing core facility[99] that provides FDA researchers and reviewers the opportunity to explore factors in the additive manufacturing process that affect product quality attributes critical for efficacy and safety. At this facility, phantoms that mimic human anatomy were constructed. They were used to evaluate devices for human imaging and for the creation of models of the mouth and throat that predict orally inhaled drug distribution in vivo.

2. Pharmaceutical and Biologics Manufacturing

- ✓ Continuous crystallization has been identified as a novel pharmaceutical technology with great potential to improve manufacturing efficiency and product quality. FDA investigated the process dynamics with and without an active control system in a continuous crystallization process and its impact on product quality. The research results will provide scientific readiness for regulatory guidance and quality standard development in the drug substance continuous manufacturing.

- ✓ To develop Process Analytical Technology (PAT) for bioreactor optimization, FDA researchers evaluated Fourier transform infrared spectroscopy for measuring key metabolites[100] and a spectroscopy-based technique for measuring viable cell density.[101] Both of these methods offer the potential for improved real-time monitoring and control of the production of complex biologics.

- ✓ FDA researchers used a quality by design (QbD) approach to assess parameters that significantly influenced glycosylation patterns of a therapeutic monoclonal antibody.[102] The research approach developed in this work allows drug developers and manufacturers to rapidly screen culture conditions in terms of their impact on critical quality attributes.

- ✓ The removal of viruses is critical in the production of a variety of biologics. FDA researchers conducted a multifaceted effort in this area and provided new insights into the failure modes for viral filters,[103] evaluated new chromatographic methods for viral clearance[104] in the production of a monoclonal antibody therapeutic, and developed strategies for incorporation of viral testing and clearance/inactivation methods into continuous processing of biologics. These research methodologies and strategies advance our ability to carry out a critical step in the production of medical products from biological material, and the removal of contaminating viruses.

- ✓ After evaluating three possible technologies, FDA scientists found that high-throughput sequencing (HTS) (also called next-generation or deep sequencing) has utility for novel virus detection. Additional laboratory investigations identified critical gaps when using HTS for safety evaluation of biologics. Efforts

to address these gaps led to the formation of an FDA-led Interest Group[105] that included representatives from regulatory agencies, industry, academia, and service providers.

- ✓ Beneficial bacteria in probiotic* products that are intended to provide a therapeutic effect may impede detection of potentially harmful microorganisms. To overcome this problem, FDA researchers developed a novel approach for detecting harmful microbes that uses viruses designed to eliminate a product's beneficial bacteria, thus allowing any potentially harmful microbes to grow unimpeded. This new technique will allow for the use of standard laboratory methods to detect potentially harmful microbes in probiotics.

- ✓ FDA researchers developed a method for making rapid and automated microscopic measurements of the size and shape of mesenchymal stem cells (MSCs).[106] This method could significantly reduce the time needed to identify MSCs that have one of the biochemical activities needed for bone growth when used in humans.

3. Developing Product Quality Standards in Critical Areas

- ✓ An FDA laboratory recently developed a risk-based, standardized, in vitro approach for testing critical properties of abuse-deterrent formulation (ADF) products,[107] including solubility in common solvents and particle size after manipulation. This research and other projects[108] on the impacts of formulation and process variables enhanced our understanding of ADFs, and supported two important guidances on these products: Abuse-Deterrent Opioids — Evaluation and Labeling[109] and General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products.[110]

- ✓ The European Pharmacopoeia is a reference work for the quality control of medicines in Europe. FDA entered into a collaborative study on behalf of the Pharmacopoeia to evaluate two versions of a test for quantifying Bet v 1, the major birch pollen allergen in allergen treatment products. In the study, both candidate tests appeared suitable. Subsequent studies led to the recommendation that one of these tests, ELISA-B, be used in quantifying allergens in products. Development of methods like these leads to improved precision with regard to dosing and clinical use of allergen treatment products. Learn more.[111]

- ✓ The mosquito-borne Chikungunya virus can cause fever, joint pain, and headache, and there is no vaccine or specific treatment. Although it is likely that Chikungunya virus could be transmitted through blood transfusions, there are no FDA-approved diagnostic or blood screening assays. FDA produced a reference reagent for the virus's RNA that can be used as a control to evaluate the sensitivity and specificity of assays for detection of the virus based on nucleic acid amplification technology (NAT). The RNA reference was characterized through a collaborative study with eight U.S. and Canadian laboratories. This reagent is now available to develop a standardized test for Chikungunya testing using NAT assays. Learn more.[112]

- ✓ The potency of newly developed inactivated influenza vaccines is tested using reagents that are prepared by FDA and used by regulators and vaccine manufacturers. This ensures standardization of vaccines made by various manufacturers. When novel H7N9 viruses emerged in China in 2013, reagents were needed to measure vaccine potency. FDA overcame a major, unexpected bottleneck in the preparation of H7N9

* Probiotic products contain microorganisms, generally bacteria, that are believed to provide health benefits when consumed.

vaccine reagents with the first use of an alternative approach to the standard procedure for producing an influenza vaccine potency reagent. Learn more.[113]

C. Ensuring the Safety and Effectiveness of Marketed Medical Products

sEven after new medical products are approved, it is necessary to continue monitoring for product-related adverse events for a variety of reasons: It may take years or decades for harmful effects of the product to manifest themselves. It is impossible to include in a clinical trial the full diversity of patients who may be exposed to the new product, including those with certain comorbidities or those with particular genetic differences that put them at higher risk of adverse reactions. And use of a product in a clinical trial may differ in crucial ways from what would be the norm in the population at large. For example, medical devices may be used in highly variable care settings, and interactions with complex technologies (such as through transmitted electrical signals) could seriously alter their function. Furthermore, the public's use of medical products may be highly conditioned by promotional materials, including direct-to-consumer advertising. Therefore, continuous monitoring of medical products as they are used by the public and in real-world settings is essential.

1. Developing Capacity for Active Surveillance of Medical Products

Traditionally, postmarketing surveillance has been accomplished by analyzing adverse event reports voluntarily submitted to the FDA by physicians and consumers (or those FDA requires from product sponsors). For drugs and biologics, these reports are collected in a structured database called FDA Adverse Event Reporting System (FAERS) and evaluated by clinical reviewers. Analogous systems are maintained for vaccines (Vaccine Adverse Event Reporting System, or VAERS,[114] which is jointly overseen by the FDA and the CDC, and for devices (Medical Device Reporting, or MDR).[115] FDA has continued to improve postmarket surveillance through these systems.

- ✓ FDA developed an algorithm for analyzing low-quality text in clinical narratives[116] that is minimally dependent on grammatical and syntactic information. This tool will save time and allow for more efficient use of reviewers' time to extract important information and analyze and make decisions about post-marketing adverse events related to medical product use. It may also guide future research in text mining of electronic health records.

FDA is also engaged in major efforts to develop *active* surveillance capabilities (active in the sense that they are not dependent on prior submission of reports to the Agency) that can be applied to electronic health records, claims data, registry information, and other kinds of "Big Data." These efforts are being supported by FDA statisticians, who are investigating optimal approaches to identifying safety signals in diverse, complex, and less than ideal data sets.

a. Sentinel

FDA launched the Sentinel Initiative[117] in 2008 to create a national electronic system for active medical product safety surveillance. In 2015, we completed the initiative's pilot phase (mini-Sentinel), whose goal was to create a fully operational postmarket surveillance tool to help us better understand the challenges of using diverse data sources to identify safety concerns. A comprehensive assessment of progress towards the objectives of the pilot is found in the Sentinel Program Interim Assessment (FY 2015),[118] which concluded that "in the implementation of Mini-Sentinel, FDA has met or exceeded the requirements of FDAAA and PDUFA."* The full Sentinel System was launched in February of 2016. Learn more about Sentinel.[119]

To advance the goals of Sentinel, FDA:

- ✓ Developed and implemented the FDA-wide Sentinel Program governance plan to enhance the surveillance activities of drug safety,
- ✓ Launched the Sentinel System's Active Risk Identification and Analysis (ARIA) process, which consists of validated programs for analyzing data from multiples sources and a common data model specifying how the database is structured,
- ✓ Used the Sentinel System in 31 medical product assessments,
- ✓ Initiated an expansion of the Sentinel Infrastructure to include data from the Medicare Virtual Research Data Center and Hospital Corporation of America, and
- ✓ Developed a way to access, use, and evaluate "fresh" data for timely influenza vaccine safety surveillance in the Sentinel group.[120] This will now be used to develop an infrastructure that works with other FDA-regulated medical products that require faster access to safety information.

b. Active surveillance efforts in medical devices

FDA continues to link and use data sources such as registries, electronic health records, and claims data, and to develop analytics with the goal of developing the capacity to assess the risks and benefits of diverse medical devices. In the Medical Device Epidemiology Network Initiative[121] (MDEpiNet), FDA and external partners are engaged in multiple projects related to methodology, infrastructure needs, and adoption of a unique device identifier-based national medical registry.

Recent accomplishments through MDEpiNet include the following:

- ✓ Through the International Consortium of Orthopedic Registries (ICOR), an international collaboration of over 30 countries encompassing over 50 real-world datasets, methods were developed to answer one analysis query among a distributed analysis network. The data in ICOR have been used to support decisions regarding safety issues related to metal-on-metal bearing surfaces for orthopedic devices.

* The Prescription Drug User Fee Act.

- ✓ In the Predictable and SuStainable Implementation of National Registries (PASSION), a series of projects were initiated to harmonize efforts to use real-world registry data for more efficient postmarket evaluation of device safety and effectiveness, and to advance implementation of novel, prospective randomized trials of new devices.

- ✓ Medical device registries containing data on large numbers of patients receiving care in diverse clinical settings are critical tools for evaluating devices in the postmarket setting. In 2015 and 2016, FDA spearheaded the creation of seven new device registries.

In 2012, FDA began to build the foundation for the National Evaluation System for health Technology (NEST).[122] The collaborative national evaluation system will link and synthesize data from different sources, such as clinical registries developed by CDRH, electronic health records, and medical billing claims, and use the data for active surveillance of devices throughout their life cycle. The current state of planning for this project including recommendations for governance, priority areas, and recommendations for initial demonstration projects are summarized in a recent report.[123]

c. Improved technologies to ensure the quality of marketed drugs and biologics

FDA has also engaged in multiple efforts to produce screening methods to better detect adulterated, misbranded, or counterfeit products. In FY 2015 and 2016, FDA researchers developed or refined the following methods to screen drugs and biologics in the field:

- Field deployable Raman spectroscopy[124]
- Surface-Enhanced Raman Spectroscopy
- Ion Mobility Spectrometry[125]
- Near infrared Spectrometry[126]
- X-ray fluorescence spectrometry

2. Examples of Research that Addressed the Safety and Efficacy of Marketed Medical Products

Surveillance systems perform a critical function in identifying potential problems with FDA-regulated medical products, but often the information provided by these systems requires follow-up. For example, a safety signal identified by querying large databases may be subject to confounding, and additional analyses may be required. In another scenario independent of systematic surveillance, the medical community may raise specific questions about product safety and effectiveness that must be addressed. Whatever the origins of the concerns, FDA reviewers tasked with assessing a variety of products in a given class are often in a position to identify crucial issues. The breadth of focused studies by FDA researchers that address the safety and efficacy of marketed medical products is beyond the scope of this report. We present some diverse examples and their impacts.

- ✓ The medical and patient communities were concerned that switching between generic versions of the antiepileptic drug lamotrigine could lead to unacceptable variations in plasma concentrations and loss of

seizure control. FDA conducted a randomized clinical trial that showed that patient exposures to the active ingredient were not affected by brand switching. The results supported FDA's bioequivalence standards. Learn more.[127]

- ✓ Thrombotic events are serious complications due to inappropriate blood clotting that can occur following administration of clotting factors. To evaluate occurrence of same-day thrombotic events for different clotting factor products and potential risk factors, FDA researchers conducted a retrospective study of individuals exposed to clotting factor products using a large insurance database. The study suggested there was an elevated risk of thrombotic events posed by several different clotting factors in patients whose factor deficiencies were not congenital. The work also underscored the importance of product and patient factors, and suggested that physicians should weigh risks vs. benefits before these products are administered to people without congenital factors. Learn more.[128]

- ✓ Post-marketing observations of vaccines show that waning immunity may result in post-vaccination infections. FDA has recently conducted studies to determine whether additional booster doses of measles-mumps-rubella (MMR) vaccine might prevent post-vaccination disease breakthrough. The analysis of the immune response after the third dose of MMR vaccine did not support a routine additional dose of the vaccine. Learn more.[129]
- ✓ Donor screening questions and blood donation testing are used to reduce the risk of transfusion-transmitted infections. The relatively high sensitivity of nucleic acid testing (NAT) used to screen donated blood for HIV has raised the question of whether such testing could substitute for the risk-based donor deferral policies. Despite the high sensitivity of NAT, it may take about nine days after infection for NAT to detect HIV. If the donated blood is HIV-positive, but NAT is negative, HIV could still be transmitted through transfusion. FDA researchers estimated the change in risk of transfusion-transmitted HIV if donor screening questions were eliminated and blood donation screening tests were the primary risk reduction measure. The model suggested that there would be an approximately fourfold increase in the risk of HIV exposure through transfusion in the United States, which indicated that there is still an important role for donor screening questions. Learn more.[130]

- ✓ Immunohistochemistry, which is a methodology that uses antibodies to detect proteins in tissue sections, is critical to personalized medicine. For example, breast cancer treatment may be guided by detection of biomarkers via microscopic examination of tissue sections. One concern in clinical medicine is the variability in the reading of such sections. FDA researchers conducted a trial to assess whether observer agreement was increased with the use of computer-aided microscopy. The study underscored the promise of computer-aided digital microscopy in reducing observer variability and improving the predictive value of biomarkers. Learn more.[131]

- ✓ In radiofrequency identification (RFID), tags are attached to various devices, and these tags can be read by special readers. These technologies are increasingly used in hospital settings to track medical devices and reduce theft. However, there is increasing evidence that RFID can interfere with medical devices. FDA scientists exposed a variety of nonimplantable devices (including syringe pumps, external defibrillators and a ventilator) to RFID readers. The testing confirmed that RFID has the potential to interfere with

critical medical equipment and suggested that medical device EMC standards need to be updated.* Learn more.[132]

- ✓ There are long standing concerns that anesthetics may have detrimental effects on the developing brain. FDA researchers developed imaging modalities in living animals to measure activation of a specific cell type in the brain (glial cells) as a marker of neurotoxicity. They observed that a widely used anesthetic increased activation, and that this effect could be mitigated by acetyl carnitine, a naturally occurring substance in the body. This work lays the ground work for improved, noninvasive evaluation of anesthetic effects on the brain, and can support more informed evaluation of anesthetic use in humans and potential risk mitigation strategies.† Learn more.[133]

3. Studies on the Public's Perception of Medical Products and the Influence of Advertising

Using a variety of approaches, including randomized trials and survey methods, FDA researchers investigate applied and theoretical issues of relevance to direct-to-consumer (DTC) and professional promotional prescription drug materials. Recent studies addressed the issue of disease information in DTC advertising and its influence on the perception of the benefits of the product,[134] the interpretation of composite outcome measures by patients and how to increase understanding of drug benefits when captured in a composite score,[135] the public's grasp of numerical data in a "drug facts box,"[136] and the factors that contribute to the effectiveness of corrective advertising.[137]

Learn more about FDA research on drug advertising.[138]

D. Advancing Regulatory Science to Promote Global Health

FDA plays a critical role in protecting the public health from threats that are chemical, biological, radiological, or nuclear (CBRN) in origin, or due to emerging pathogens. Our efforts to ensure that medical countermeasures, including drugs, biologics, vaccines, and diagnostic tests are safe, effective, and secure, were formalized in the Medical Countermeasures Initiative.[139] FDA researchers focus on promoting the development of medical countermeasures by identifying and resolving complex regulatory science challenges, and through development and evaluation of new concepts, methods, models, and reagents to enhance safety, effectiveness, quality and consistency. In an increasingly interconnected global economy, and with rapid movement of people across national boundaries, health security issues are global in scope. We coordinate our efforts with organizations such as the World Health Organization (WHO), as well as national and international regulatory agencies.

* FDA is working to develop RFID simulators that could be the basis for an RFID test standard.

† In December of 2016, FDA issued a safety warning stating that repeated or lengthy use of general anesthesia or sedation drugs for children younger than 3 or pregnant women in their third trimester may affect youngsters' developing brains.

1. Recent Research Accomplishments in Combatting Ebola, Zika, and Influenza Viruses

a. Ebola virus

In an outbreak in West Africa that lasted from 2013 to 2016, the Ebola virus caused over 10,000 deaths. FDA has played a key role in the development and review of investigational vaccines and therapeutic products by initiating projects to improve neutralizing antibody assays to support vaccine and therapeutics development, developing reference standards and reagents to support development of accurate diagnostic and vaccine potency assays, and helping to elucidate correlates of protection and bridge immune responses to humans.

- ✓ FDA researchers developed human polyclonal antibodies that are protective and neutralizing in a mouse model against Ebola virus and can be produced in high quantities in transchromosomal cattle. This approach to development of antibody-based therapeutics has advantages in terms of safety and efficacy relative to other approaches, and represents a promising path for developing therapeutics for other emerging pathogens. Learn more.[140]

- ✓ FDA researchers studied a subunit vaccine containing the extracellular domain of the Ebola virus glycoprotein formulated with different adjuvants. The preparations elicited varied protection and suggested the potential for development of a vaccine for human use. Learn more.[141]

- ✓ FDA held a workshop to discuss the important aspects of Ebola virus pathogenesis and vaccine immunology[142] and published two papers reviewing current work on vaccine efficacy[143] and immunology[144] to inform future clinical, scientific and regulatory decision making related to vaccines against Ebola. FDA also published the guidance *Recommendations for Assessment of Blood Donor Suitability, Donor Deferral, and Blood Product Management in Response to Ebola Virus.*[145]

b. Zika virus

Since 2015, the mosquito-borne Zika virus has caused microcephaly in more than 2000 children in South and Central America*, and has recently spread to Florida and Texas. In addition to facilitating the development of vaccines and treatments, FDA research has focused on protecting patients receiving blood and other products from Zika infection.

- ✓ FDA researchers have developed RNA reference standards for use in diagnostic and blood screening assay development, and for testing vaccines, and other therapeutics. These reference standards were adopted by the WHO as International Reference Materials and are being used by developers of blood screening and diagnostic tests for analytic validation.

- ✓ FDA scientists constructed a cDNA clone of Zika virus that could grow inside a mammalian cell. This construct *(*a short circular piece of DNA containing the virus's genetic sequence) in which key components of the RNA virus are easily modified, can be used in studies aimed at the development of Zika vaccines and therapeutics. Learn more.[146]

* Pan American Health Organization (www.paho.org/hq/index).

- ✓ FDA researchers developed a mouse model of Zika infection to better characterize the effects of the virus on the central nervous system and the immune response to infection. The model can be used for detailed mechanistic studies of Zika-virus related pathologies, including long-term effects of infection, and assessment of vaccines and therapeutics.

- ✓ FDA published multiple guidance documents related to protecting the blood supply and tissue donations from Zika virus.

c. Influenza

Annual outbreaks of the flu typically result in 3 to 5 million cases of severe illness and about 250,000 to 500,000 deaths.[147] The virus causing the disease evolves rapidly. In June 2009, the WHO declared an outbreak of a new type of influenza A/H1N1 to be a pandemic.

FDA's efforts to address the threat of influenza include the following:

- ✓ Modeled flu transmission and evolution in populations protected with cross protective flu vaccines[148] (i.e., vaccines that protect against influenza viruses with genetic differences) and studied such vaccines in a mouse model.[149] The work suggested that cross-protective influenza vaccines may represent a valuable public health option in response to a flu pandemic.

- ✓ Developed and established the consistency across different laboratories of a new assay to characterize immune responses to candidate flu vaccines. Learn more.[150]

- ✓ Optimized assays based on next-generation sequencing that can be used for monitoring of changes to influenza viruses over time. These assays will permit identification of a broad range of influenza viruses and the monitoring of emerging strains with pandemic potential, thereby facilitating diagnostics and antiviral treatments. Learn more.[151]

- ✓ Modified sequences of the seed virus used to produce flu vaccines for manufacturing pandemic influenza vaccines to increase yields.

- ✓ Published a review article: An overview of the regulation of influenza vaccines in the United States.[152]

2. Other Accomplishments in Global Health

- ✓ FDA researchers explained the cellular defense mechanisms activated by infection with *F. tularensis*. Learn more.[153]

- ✓ A cell-based method was developed to evaluate protective immune response to vaccines against *F. tularensis.* The method will facilitate screening of vaccines for this rare disease in terms of effectiveness and its potential as a bioterrorism agent. Learn more.[154]

- ✓ FDA researchers developed a platform based on microarray technology that allows for detection and identification of 97 blood-borne pathogens in a single test. This and similar platforms promise to reduce the risk of transfusion-mediated spread of emerging diseases. Learn more.[155]

- ✓ To fill a critical regulatory science gap for microbial genomes that are underrepresented in existing collections, the FDA worked collaboratively to establish a reference database[156] of regulatory-grade quality sequences from diverse infectious microorganisms. The database will function as a tool for clinical validation of infectious disease diagnostic devices.

- ✓ FDA researchers developed a standard, reproducible technique for "spiking" human blood or other fluids with a sample of known concentration and type of bacteria or virus to serve as a substitute for a clinical sample. This technique provides industry with an approved method that supports development and approval of diagnostic platforms for detecting pathogens in clinical specimens. Learn more.[157]

- ✓ Antibiotics and antiviral and antimalarial drugs have often been attractive targets for counterfeiters, because these drugs are often used in emergency situations such as outbreaks or pandemics where the supply of bona fide drugs may be limited. FDA researchers developed an approach to support rapid screening of these products using spectroscopic methods based on a library containing spectra of the active ingredient in each product. This new approach provides a first-pass screening method to identify suspicious samples without having prior spectral information on the full range of samples that may be encountered in emergency settings.

- ✓ Disease outbreaks can be associated with contaminated devices. FDA has recently developed advanced sensing methodologies based on novel fiber-optic Fourier transform infrared spectroscopy for detecting and identifying contaminants of optical diagnostics and other devices. The sensing methodologies make possible real-time, on-site detection of microorganisms and toxins, and are intended to support antimicrobial management, detecting and tracking of disease outbreaks, and investigation of unknown pathogens. Learn more.[158]

- ✓ FDA-regulated facemasks and respirators form the first line of defense against any airborne pandemic or airborne bioterror attack. Leakage through the gaps between the wearer's face and personal protective equipment (PPE) is the largest factor in exposure. FDA researchers have developed models to assess PPE-related risks to different age groups in case of a pandemic or a bio-terror attack. Learn more.[159]

When disease outbreaks and bioterrorism events occur, it is important that personnel in the field can communicate with the Agency. Thus, FDA is building software for a system—Real-time Application for Portable Interactive Devices (RAPID)— a prototype mobile platform-based multimedia system based on smart phones and their respective applications. The goal is to provide a web- and cloud-based bidirectional communication and information system to respond to medical countermeasure events. Learn more.[160]

2015-2016 accomplishments in the RAPID initiative included the following:

- ✓ Creation of a cloud-based adverse event reporting system which may be used in national emergencies

- ✓ Creation of a bidirectional Risk Evaluation and Management information and analytic system

- ✓ Installation of the RAPID II cloud version in Gov Cloud

E. Infrastructure and Organizational Changes to Advance Regulatory Science

Over the past two years, we have improved the effectiveness and efficiency of our science programs by consolidating our organization and programs at the FDA's White Oak Campus in Silver Spring, Maryland and enhancing our scientific infrastructure. We have created new software tools, resources, and knowledge management systems to support review activities. Our research partnerships have made significant advances in support of medical product development, and we have established new Centers of Excellence and research consortia. Through participation of our staff at workshops, Critical Path Innovation meetings, and other scientific forums, we have extended our outreach to the scientific community, medical product developers, patient advocates, and the public.

1. Scientific Infrastructure

a. Consolidation of the White Oak animal programs

In 2016, to increase efficiency and consistency of oversight and management of animal-based research, FDA consolidated two vivarium programs into one. The consolidation eliminated one Animal Care and Use Committee, combined multiple contracts into one, and uses a single administrative unit that currently supports approximately 100 principal investigators involved with over 200 active protocols. The White Oak Animal program supports FDA conduct of animal studies to evaluate the safety of drugs, vaccines and other biologics, and medical devices. It also supports development and evaluation of animal models to facilitate evaluation of new product areas (see Section A.2.d).

In addition, the program allowed for critical improvements in scientific capabilities, including the addition of a small animal MRI and CT scanner that enable non-invasive, longitudinal visualization on desired endpoints. In April 2015, BSL-3 and Animal BSL-3 laboratories[*] were certified for use to support research on important pathogens relevant to our regulatory portfolio (i.e., pandemic strains of influenza, *Mycobacterium tuberculosis*, Human Immunodeficiency Virus, Chikungunya virus, agents of transmissible spongiform encephalopathies, etc.).

b. Creation of the Shared Resources Program

FDA regulates products that increasingly rely on sophisticated and complex equipment for their manufacture or characterization. To make cutting-edge but expensive technology available to multiple Centers and improve efficiency, FDA's Senior Science Council developed the Shared Resources Program.

[*] One that is suitable for work with laboratory animals infected with indigenous or exotic agents, agents that present a potential for aerosol transmission, and agents causing serious or potentially lethal disease.

This program creates and oversees development of sustainable, FDA-wide shared resources through specific cost-sharing models. Shared resources include large scientific equipment (e.g., mass spectrometers, MRI, etc.), core facilities for certain technologies (e.g. 3-D printing, confocal microscopy), and widely used scientific software or data sources. Furthermore, the program has enabled our Centers to purchase and jointly manage new resources that support cross-center interests. For example, through this program, FDA established an additive manufacturing core (3-D printing facility) that provides FDA scientists and reviewers with firsthand access to and more detailed knowledge of this transformative technology.

c. Scientific computing

As noted in the 2013-14 Progress Report, FDA medical product centers have developed two high-performance computing (HPC) capabilities—the CDRH HPC facility and the High-Performance Integrated Virtual Environment[161] (HIVE).

The CDRH HPC facility supports work in modeling and simulation (relevant to cardiology and toxicology), genome analysis (relevant to personalized medicine), fluid dynamics analysis, Bayesian analysis (as applied to adaptive clinical trials and real-world data), risk assessments, and text mining of adverse event reports and patient records. In response to scientists' requests, over 130 software programs have recently been deployed on the cluster. This facility has enabled computer modeling efforts in FDA to achieve simulation speed increases of between 100 and 1,000 fold for some applications, allowing Agency scientists to run simulations in days that would take years on a workstation. Use of the HPC environment has grown by 50% in each of the past two years.

HIVE is a private, cloud-based environment that comprises both a storage library of data and powerful computing capacity. It is being used to independently analyze next-generation sequencing data in regulatory submissions, but it also hosts approximately 80 research projects. In FY 2015-2016, over 150 new users registered and used HIVE resources.

Advances in 2015-2016 of HIVE capabilities include the following:

- ✓ Expansion and development of utilities to support evaluation of data from mass spectrometry for proteomics and glycomics*
- ✓ Programming to support a new initiative to monitor adverse events in medical devices by pooling and analyzing multiple data streams
- ✓ Development of computing resources to support implementation of the National Evaluation System for Health Technology (NEST) at CDRH (see description in section A.1.b), including tools to support the "Big

* Proteomics and glycomics refer to systematic, large scale, quantitative analyses of the proteins and complex sugars, respectively, in an organism.

Data" analytic and visualization techniques to continuously evaluate real-world data on medical devices and clinical outcomes

- ✓ Construction of analysis software that takes advantage of the supercomputer infrastructure to provide results in near-real time

2. Advances in Data Standards and Review Tools and Resources to Support Scientific Review

a. Data standards

Establishing common standards for data reporting provides new opportunities to transform the massive amounts of data from clinical studies on specific diseases into information that can be easily grouped for reporting and analysis. In October 2015, FDA published the third version of the Therapeutic Area (TA) Standards Initiative Project Plan,[162] which guides all major aspects of our multi-year initiative to develop and implement TA standards to support the regulatory review process. The list of the prioritized TAs and their development status was revised to reflect progress made and changes in CDER priorities. Of the 54 TAs on this list, 42 are already being used at FDA to capture business needs, or are under development with external parties.

In the nonclinical area, a pilot team successfully executed its plan to receive sample data for review and to support ongoing implementation efforts. FDA also published an update of the validation rules for Standard for Exchange of Nonclinical Data (SEND) formatted files.

b. Tools and knowledge management systems to support review of medical product applications

Software tools to support enhanced review

- ✓ A new system (Electronic Managed Review Process, or eMRP) was implemented to enhance and automate review process of regulatory submissions for biologics.
- ✓ JumpStart is a service that provides new drug application (NDA)/biologics license application (BLA) Review Teams with clinical trial data analyses early in the review process to assess data composition, quality, analyses options, and tools for the analyses—so reviewers have the information to conduct an effective evaluation of the drug submission. In 2015-16, Jump Start supported Office of New Drugs reviewers with 60 full JumpStart services.
- ✓ A review tool called DataFit was developed to assess data standards compliance in review submissions. The tool enables reviewers to rapidly assess whether the data submitted with NDAs are "fit for use." In FY2015, it was applied to 72 studies submitted to the FDA.
- ✓ FDA created FDALabel[163] to allow reviewers to perform customizable searches of the entire labeling text of prescription drug and biological products and over-the-counter drugs. For the review of drug applications, it has been used by approximately 200 unique users per month since implementation.

3. Organizational Changes to Further Research Capacity and Coordination

In January 2015, FDA established the Office of Pharmaceutical Quality (OPQ)[164] within the Center for Drug Evaluation and Research (CDER). The office combines oversight of product quality and manufacturing for drugs, protein biologics, biosimilars and generic drugs, and is designed to integrate science and research findings into review, inspection, and surveillance across the product lifecycle. The laboratories of OPQ conduct mission-directed, collaborative laboratory-based science and research activities to support the development of scientific standards and policies for safe and effective, high-quality drug products, as well as the Emerging Technology Program for modernizing pharmaceutical manufacturing.

At the CDRH, FDA piloted a Health Regulatory Science Research Program Review to facilitate a feedback loop between reviewers and bench scientists. In this program, scientists present high-impact research relevant to a clinical area (e.g., radiology or cardiology) and regulatory reviewers have an opportunity for in-depth scientific conversation and feedback to ensure regulatory science is aligned with regulatory needs. Scientific programs will receive input on regulatory impact, public health implications, and suggested future directions. The Regulatory Science Subcommittee has been proactively enhancing medical device innovation, development, safety, quality, and effectiveness by developing policies and practices to promote the identification and incorporation of new science and technology into regulatory decision making. The Regulatory Science Subcommittee published regulatory science priorities[165] for medical devices in 2015 and 2017.

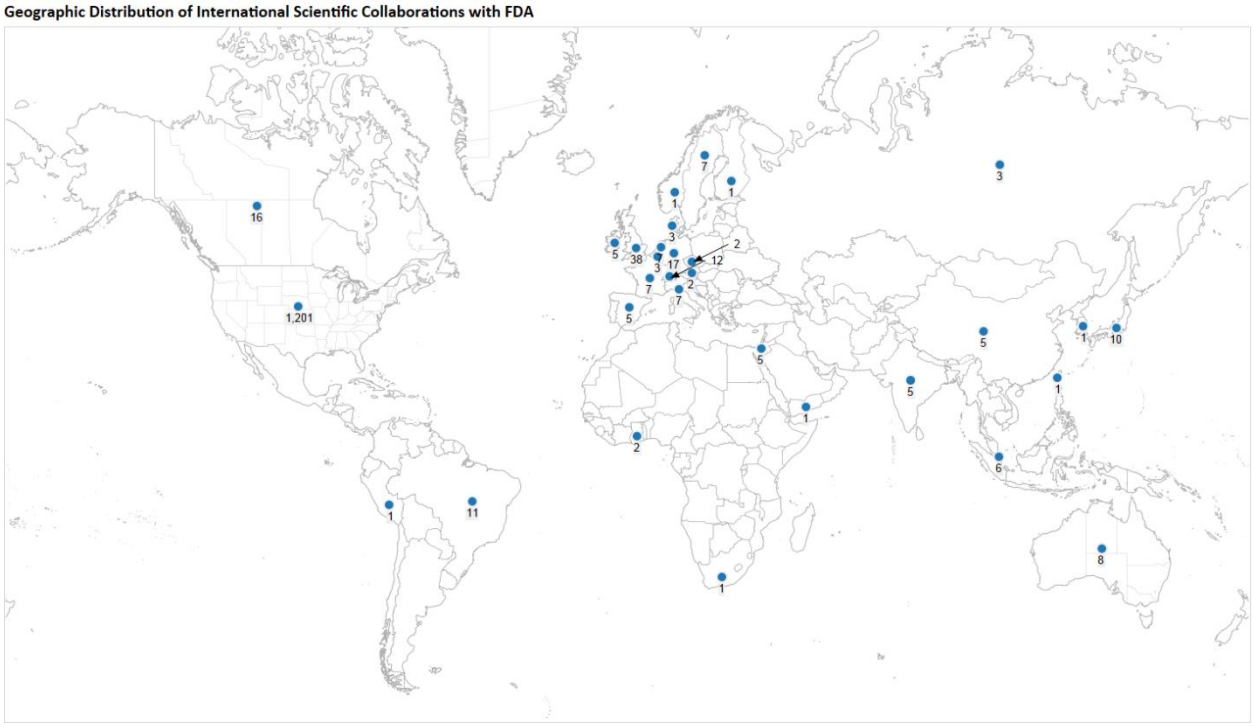
Based on an independent review of its research programs, several changes were made at the Center for Biologics Evaluation and Research (CBER) to enhance research oversight. First, a Regulatory Science Council was created and tasked with oversight across research activities. Second, internal scientific peer review of individual research projects was scheduled for once every four years for each program, and the peer review committee's role was revamped so that it was advisory to the offices. Third, a Resource Committee was created to provide guidance and general oversight on budget execution. Fourth, the annual research reporting database was modified to better align research projects to office objectives. Finally, a Research Dashboard was instituted to enable regular and periodic review of research budget and support management decisions.

a. Scientific research collaborations

The formation of consortia to help address specific scientific gaps has proved to be an effective means of supporting medical product development tools. These public-private partnerships participate in wide- ranging research collaborations at the national and international level, and new policies and procedures have been developed to assure transparency in FDA's interactions with them. In 2015, we launched the International Neonatal Consortium, a global collaboration focused on the safety and effectiveness of therapies for neonates.

The FDA Centers of Excellence at the University of Maryland, Georgetown University, the University of California San Francisco, in a joint effort with Stanford University and Johns Hopkins University, have worked to address critical gaps in regulatory science. A newly established Center at Yale University, in a joint effort with Mayo Clinic, will develop methods to use diverse data, including, genomic and biobank information, to support regulatory decision-making and build FDA's capacity to deploy advanced analytic methods. Furthermore, FDA's Broad Agency Announcement (BAA) or Program for Extramural Regulatory Science and Innovation (PERSI-BAA)[166] encourages participation by science and technology-based firms and educational institutions in advancing a variety of areas in regulatory science. The BAA program has sustained a consistent growth in the number of contract awards: 29 new projects were awarded in FY 2015, and 10 were completed.

In addition to these formalized collaborations, FDA scientists continuously engage with the scientific community through informal collaborations with academic, governmental (state, Federal, international), non-profit, and for-profit organizations.



FDA Scientific Collaborations include Academic, For-Profit, Non-Profit, and Governmental Partners (See Appendix for map of US FDA Collaborations)

b. Enhancing Scientific Communication

Our researchers publish extensively, not only to convey the results of their research efforts, but also to explain FDA's current scientific thinking on medical product development and approvals. (FDA publications are tabulated by Center and year in the Appendix.) We also engage the scientific

community through scientific symposia (including the FDA Science Forum[167]) and scientific workshops and advisory committee meetings.

FDA also has many long-standing scientific interest groups with a history of facilitating interaction among experts across centers. In 2015, to accelerate these interactions and identify new opportunities for cross-cutting scientific exchange, the Office of the Chief Scientist began providing support for scientific working groups to develop workshops and seminars. In addition to long-standing working groups like the FDA Statistical Association and the FDA Genomics Working Group, the program has added five new groups in important areas such as biomarkers, modeling and simulation, additive manufacturing, and the microbiome.*

In addition, FDA engages external scientific community through targeted scientific workshops.[168]

The Critical Path Innovation Meeting (CPIM) Program[169] 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. In 2015, FDA issued a guidance[170] describing the purpose, scope, documentation, and administrative procedures for a CPIM and delineating appropriate topics for such meetings. In FYs 2015 and 2016 FDA convened 33 CPIM meetings.

Critical Path Meetings held to date[171]

* Individual scientific working groups supported by FDA's Office of the Chief Scientist in 2015-2016 focused on additive manufacturing, biomarkers, emerging sciences, genetics and genomics, the microbiome, modeling and simulation, nanotechnology, social and behavioral sciences, standards, statistics, and toxicology. Major activities included workshops, lecture series, and specific training for FDA staff.

F. Appendix

National Distribution of FDA Scientific Collaborations with Academic, For-Profit, Non-Profit, or Governmental Partners. (There are no formal partnerships in Alaska or Hawaii.)

1. Examples of Consortia with FDA Involvement

Consortia	Partners	Mission	FY 2015-2016 Key Accomplishments
The Analgesic Clinical Trial Translations, Innovations, Opportunities and Networks Initiative (ACTTION)[1]	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	Published 13 peer-reviewed papers in the area of clinical trial methodologies for analgesics, anesthetics and addiction treatment. Two of the publications leveraged the ACTTION-piloted shared data platform called Resource for Evaluating Procedures and Outcomes of Randomized Trials (REPORT) database Held the 19th meeting of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) to develop recommendations for accelerating the development of precision pain medicine Developed the Public Relations and Other Communication and Education Strategies (PROCESS) Working Group for increased communication of ACTTION deliverables

Biomarkers Consortium (BC)[2]	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	Published 4 peer-reviewed papers on developing biomarkers for 1) knee osteoarthritis, and 2) pancreatic beta cell function for tracking diabetes progression The innovative, adaptive I-SPY-2 Trail, which was launched by BC, published results of Phase II trial and two therapies are moving to Phase III trials Developed and experimentally validated a targeted mass spectrometry approach to identify and evaluate Alzheimer's Disease biomarkers for early identification of mild cognitive impairment that will progress to Alzheimer's Disease. This early identification will allow for early therapeutic intervention through clinical trials Collaborated with FDA to host workshop on developing the evidentiary considerations for developing safety biomarkers
The Coalition Against Major Disease (CAMD) Consortium[3]	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 the data to support use of 1) cerebral spinal fluid (CSF) analytes and 2) hippocampal volume as biomarkers for early identification of Alzheimer's Disease to support patient enrollment into clinical trials. These biomarkers received FDA Letters of Support Received 'Fit for Purpose' Designation from FDA of a quantitative model describing the natural history of the cognitive change in Alzheimer's Disease. This model can be used to inform clinical trial parameters such as dose selection and study duration Developed an Alzheimer's Disease clinical trials database to enable analysis and development of new drug development tools Developed methodology to harmonize Alzheimer's Disease Clinical Data Interchange Standards Consortium (CDISC) standards across case reports in Alzheimer's Disease prevention clinical trials
The Clinical Trials Transformation Initiative (CTTI)[4]	Multiple government agencies; pharmaceutical, biotech, device and clinical research organizations, individual patients and patient advocacy groups, professional societies; IRBs, clinical investigators, and academic institutions	To develop and drive adoption of practices, that will increase the quality and efficiency of clinical trials.	Developed recommendations for clinical trial conduct including: 1) optimizing the use of central Institutional Review Boards (IRB) for multicenter clinical trials 2) enhancing the quality of clinical trial operations 3) efficient and effective clinical trial recruitment planning 4) effective engagement with patient groups around clinical trials 5) improving the informed consent process and document 6) best practices for data monitoring committees 7) designing key training elements for good clinical practice (GCP) for investigators 8) desired attributes of electronic portals for expedited safety reporting 9) how to streamline protocol elements for hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia (HABP/VABP) trials 10) how to optimize the operational efficiency of data collection in HABP/VABP trials

The Critical Path to TB Drug Regimens (CPTR) Consortium[5]	Bill & Melinda Gates 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	Received qualification of Hollow Fiber Model as a preclinical tool for tuberculosis drug development from the European Medicines Agency (EMA) Developed database containing genome sequences from mycobacterium tuberculosis strains. This database can be used to identify drug resistant tuberculosis Developed publicly available data-sharing platform of curated and standardized Phase III tuberculosis clinical trials to inform novel tuberculosis drug regimens
Cardiac Safety Research Consortium (CSRC)[6]	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	Published 3 peer-reviewed papers on cardiovascular safety considerations throughout drug development, including 1) AdvaMed Dual-Antiplatelet Therapy for 1 year after placement of drug-eluting stent reduces risk of stent thrombosis and other major adverse events, 2) robust early QT assessment in early phase clinical trials can replace thorough QT study, 3) radial access site leads to enhanced quality of life as compared to femoral access Hosted 5 stakeholder meetings to develop recommendations for cardiovascular safety trials, such as 1) clinical development of specific new oral anticoagulant reversal agents, 2) methodologies for cardiovascular safety outcome trials , 3) considerations for cardiovascular safety for anti-diabetes drugs, 4) cardiovascular safety concerns for new cell therapies Developed collaborative think tank to promote dialogue on the cardiac safety area across a very broad base of stakeholders, from patients and doctors to manufacturers and regulators
The Polycystic Kidney Disease Outcomes (PKDOC) Consortium[7]	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	Developed data to support use of total kidney volume (TKV) as prognostic biomarker to enable early identification of autosomal dominant polycystic kidney disease (ADPKD) and support patient enrollment in clinical trials. TKV received both FDA and EMA regulatory qualification Developed database containing three patient registries (from University of Colorado-Denver, Mayo Clinic, Emory University) to enable pooled analysis of large datasets to inform future ADPKD clinical trials Completed 'Development of 'Polycystic Kidney Disease Therapeutic user guide' to provide a clinical data standard for regulatory submission

The Patient Reported Outcome (PRO) Consortium[8]	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 webinar series to disseminate recommendations and best practices for determining clinical significance of changes in patient reported outcomes. Published 2 peer-reviewed publications outlining methods for the development of patient reported outcome measures for 1) mild cognitive decline due to Alzheimer's disease, and 2) major depressive disorder clinical trials (dysphoria, appetite and sleep changes, cognitive changes) Submitted Clinical Outcome Assessments (COA) for regulatory review for the following disorders: Irritable bowel disease, Major depressive disorder, Asthma, Non-small cell lung cancer, Functional dyspepsia, and Alzheimer's Disease
The Predictive Safety Testing Consortium (PSTC)[9]	FDA, EMA and the Pharmaceuticals and Medical Devices Agency (PMDA, the governmental organization in Japan that regulates medical products), 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 preclinical use of rat biomarkers for drug-induced skeletal muscle injury, and received a FDA Letter of Support
International Serious Adverse Events Consortium (iSAEC)[10]	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	Using iSAEC data sharing model, published data identifying genetic associations with drug-induced toxicities. These genetic associations can be leveraged to inform drug development and patient treatment decisions. In particular, iSAEC uncovered 1) an association between genetic changes in Class II HLA region and thiopurine-induced pancreatitis in patients with irritable bowel disease (IBD), 2) a correlation between a HLA region and 5-aminosalicylate kidney injury, and 3) a significant correlation between an HLA haplotype with flupirtine-induced liver injury Leveraged electronic medical record databases and conducted a study to reveal that substantial weight gain is significantly correlated with antipsychotic medications. iSAEC recommended classification of weight gain as an adverse health event Developed recommendations for diagnostic standards for drug-induced kidney disease

SmartTots[11]	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	Funded research that led to an enhanced understanding of the impact of anesthetics in developing brains, such as studying effects of anesthestic exposure before age 3 on neurocognitive function and behavior Updated the SMARTTots consensus statement on the use of Anesthetic and Sedative Drugs in Infants and Toddlers. This statement educates healthcare workers and parents about the potential risks
Medical Device Innovation Consortium (MDIC) [12]	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	Awarded the Coordinating Center for the National Evaluation System for health Technology (NEST) Virtual Patient Proof-of-Concept demonstrating the statistical model can reduce clinical study timelines by nearly 50% Released a Blueprint for US Early Feasibility Study Success, which includes best practices guidelines for planning and conducting an Early Feasibility Study. Delivered the Case for Quality Change Adoption Plan, a report that provided a view of the current state of implementation of the quality system maturity model and other key initiatives, and set the vision for tomorrow Released the Patient Preference Framework Report, which details a framework for incorporating information on patient preferences regarding benefit and risk into regulatory assessments of new medical technology Held 11 MDICx series teleconference workshops and their third Annual Public Forum featuring emerging trends in medical technology regulatory science
HESI Cardiac Safety Technical Committee[13]	Academia, FDA and industry	Improve prediction of drug-induced cardiac safety issues	Published 2 peer-reviewed papers validating preclinical models for assessing drug-induced effects on cardiac function. Preclinical models include non-rodent animal models (guinea pigs, rabbits, dogs, non-human primates) Continued to support the Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative
National Institute for Pharmaceutical Technology and Education (NIPTE)[14]	Academia, FDA, 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	Published 9 peer-reviewed papers on improving drug formulations and product quality, including 1) validating model systems for biosimilarity analysis, 2) understanding the nature of cocrystallization, 3) studying nonlinear optical Stokes ellipsometric (NOSE) microscopy for rapid discrimination of active pharmaceutical ingredients and, 4) studying second harmonic generation (SHG) microscopy-guided synchrotron powder X-ray diffraction (PXRD) method for the detection of trace crystalline active pharmaceutical ingredients

Multiple Sclerosis Outcome Assessments Consortium (MSOAC)[15]	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	Leveraged newly developed clinical data standard to create MS Placebo database to offer a central standard set of clinical observations and inform future clinical trial design. This dataset can assist in the development of new therapies that will delay or reverse symptoms of MS In active discussions with the FDA Clinical Outcome Assessment Qualification Program regarding development of a new clinical outcome assessment instrument for use in clinical trials of medical products to treat MS
Coalition For Accelerating Standards and Therapies (CFAST)[16]	Clinical Data Interchange Standards Consortium (CDISC) 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	Released therapeutic area data standard user guides for the following therapeutic areas: 1) cardiovascular studies 2) influenza 3) QT studies(drug-induced cardiotoxicity) 4) schizophrenia 5) hepatitis C 6) dyslipidemia 7) chronic obstructive pulmonary disease 8) general viral resistance 9) traumatic brain injury 10) tuberculosis
Innovation in Medical Evidence Development and Surveillance (IMEDS) program[17]	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	Published 3 peer-reviewed papers on development of methodology for study design in the post-market setting and algorithms to identify health outcomes using electronic health records Produced 21 webinars and presentations to disseminate ideas surrounding the development of science and tools to support post-market evidence generation
Product Quality Research Institute (PQRI)[18]	Academia, industry, and FDA	Generate and share timely, relevant, and impactful information that advances drug product quality and development	Published peer-reviewed papers on properties of drug excipients to inform regulatory requirements for drug formulations Hosted 2nd annual FDA/PQRI conference to review 1) emerging regulatory initiatives, 2) regulatory submission, assessment, and inspection, 3) product and process development, and 4) manufacturing, risk management, and quality assurance Hosted workshop on developing recommendations and research priorities for defining elemental impurity requirements in global environment Supporting development of FDA guidances on pharmaceutical manufacturing including 1) Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products, 2) Liposome Drug Products, 3) Elemental Impurities in Drug Products, and 4) Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification Systems Class 1 and 3 Drugs

Institute for Safe Medication Practices (ISMP) [19]	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	Provide ongoing publication of electronic biweekly newsletter (ISMP Medication Safety Alert) by e-mail covering current medication alerts, device errors and adverse drug reactions to all health care delivery settings Issued 2015 and 2016 updates on the Joint-commission medication-related standards, a webinar to inform hospital and health systems to minimize medication errors Produced and distributed educational webinars on a range of key medication safety topics
MicroArray Quality Control-IV (MAQC-III)[20]	Major providers of microarray platforms and RNA samples, NIH, FDA, 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	A concept paper covering the new MAQCIV project, known as Sequencing Quality Control Phase 2 (SEQC2), was approved in 2015. Information regarding the SEQC2 project was communicated to all the FDA centers, and representatives from the medical product centers have joined the project development. The first public workshop to communicate this project with the research community was held at NIH Sept 13-14, 2016 and attended by 180 scientists from across the country.
Kidney Health Initiative (KHI)[21]	Patient organizations, health professional organizations, research institutions, foundations, pharmaceutical, biotechnology and device manufacturers, dialysis providers, and U.S. 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	Published 3 peer-review papers to 1) identify barriers and solutions to stimulate innovation of new treatments for kidney disease, 2) develop recommendations of methodology to determine pharmacokinetic parameters and dosing recommendations for common pharmaceuticals used by Continuous Renal Replacement Therapy (CRRT) patients, and 3) develop recommendations on implementation strategies to embed clinical trials for dialysis into health care delivery. Developed KHI Patient and Family Partnership Council to provide platform for patients to engage in developing recommendations to enhance patient safety and quality
International Neonatal Consortium (INC)[22]	Pharmaceutical industry, patient and nurse advocacy organizations, government and regulatory agencies, academia	Accelerate the development of safe, effective therapies for newborns	Hosted 2 workshops to discuss and prioritize consortium efforts to apply regulatory science to neonates. Set up 4 working groups to focus consortium efforts. The working groups are 1) clinical pharmacology in neonates, 2) data infrastructure and data sharing, 3) bronchopulmonary dysplasia, and 4) seizures clinical trial protocols
Duchenne Regulatory Science Consortium (D-RSC)[23]	Academia, pharmaceutical industry	Convene de-identified data to understand the variability seen in Duchenne's muscular dystrophy and develop a Duchenne progression model. Once developed, this model will provide predictive value to the design of clinical trials	Developing natural history database and a disease stimulation model for Duchenne muscular dystrophy

Critical Path for Parkinson's (CPP)[24]	Academia, pharmaceutical industry	Establish best practices and more efficient protocols for planning and designing clinical trials in early Parkinson's disease	Developing imaging biomarkers for Parkinson's Disease to allow clinical trial enrichment of patients with both dopamine deficiency and early stage motor impairments for Parkinson's Disease clinical trials
Global Pediatric Clinical Trials Network Pre-Launch Consortium (PTC)[25]	PTC leadership team	Form an independent non-profit entity that operates a novel global pediatric clinical trials network. The consortium is charged with establishing the network, creating its organizational and operating framework, and identifying its leadership team	Developing an advisory report and recommendations to support collaborations between the Critical Path Institute and a newly formed non-profit that will manage the pediatric clinical trial network
Advanced Virus Detection Technologies Interest Group (AVDTIG)[26]	The Advanced Virus Detection Technologies Interest Group (AVDTIG) is a joint effort led by regulatory and industry scientists that includes participation from national and international representatives from regulatory and other government agencies, biopharmaceutical industries, technology service providers, and academia	The mission of the group is to facilitate discussions and provide a forum for sharing data and experiences using advanced new virus detection technologies, with a focus on high throughput sequencing technologies	Completion of a spiking study conducted by three labs (including CBER) to evaluate sensitivity of virus detection by different sequencing platforms Development of reference virus stocks by a CBER lab for performance evaluation of high throughput sequencing, which can aid in method standardization Some members of the AVDTIG participated in evaluation of bioinformatics pipelines using a research dataset provided by a CBER lab Some members of the AVDTIG participated in evaluating the efficiency and robustness for virus detection of a draft new virus database being developed by a CBER lab
External Quality Assurance Proficiency Oversight Laboratory[27]	Academia and government	The External Quality Assurance Proficiency Oversight Laboratory of Duke University coordinates a multi-center, international effort sponsored and funded by the National Institute of Allergy and Infectious Diseases to support the development, implementation and oversight of external quality assurance programs that monitor laboratories involved in HIV/AIDS research and vaccine trials around the world	FDA participated in the collaboration to characterize over 50 HIV variants among seven international sites to develop a globally diverse, dynamic and well characterized HIV variant panel for diagnostics, vaccine and therapy evaluation

America Makes[28]	DoE, US Army, US Air Force, NASA - See membership list	As the national accelerator for additive manufacturing (AM) and 3-D printing (3DP), America Makes is the nation's leading and collaborative partner in AM and 3DP technology research, discovery, creation, and innovation. Structured as a public-private partnership with member organizations from industry, academia, government, non-government agencies, and workforce and economic development resources, we are working together to innovate and accelerate AM and 3DP to increase our nation's global manufacturing. competitiveness	Began a Standards Coordination effort to increase efficiency and practicality of standards being developed in this area Reviewed proposals for funding by the overall organization
Medical Device Epidemiology Network (MDEpiNet)[29]	Over 100 partners including academic organizations, healthcare organizations, medical device industry partners, patient groups, and the regulatory industry	As a Public Private Partnership (PPP), MDEpiNet is working to improve and integrate real-world data infrastructure, develop appropriate methodologies, and conduct studies to improve patient-centered outcomes for medical devices around the world	Built sustainable PPP with over 100 partnering organizations and implemented financial model for supporting PPP functions; Via MDEpiNet Predictable and Sustainable Implementation of National (PASSION) Registries, built interdisciplinary coalition of stakeholders involved in peripheral vascular arena; developed common data model and global case report form for the future interoperable registry platform; in the process of planning the nesting of the first clinical trial in peripheral vascular registry; Via MDEpiNet Science and Infrastructure workstream, continue to develop strategically Coordinated Registry Networks (CRNs) in orthopedic and vascular fields by linking national registries to claims data, PCORNet, Sentinel and Medicare data; Built coalitions and held targeted multi-stakeholder think tanks in the following areas (1) Active Surveillance; (2) Return on Investment when using registries for evidence generation; (3) Development of CRN for obesity treatment devices; (4) Development of CRN for high frequency ultrasound for prostate ablation; (5) Venous Access National Guideline and Registry Development (VANGUARD), and (6) UDI implementation (BUILD); Via MDEpiNet Patient and Family Engagement Program held first patient-led round table focused on Temporo-Mandibular Joint Implants safety; Applied the DELTA (Data Extraction and Longitudinal Trend Analysis) and software for prospective active surveillance in the National Cath PCI registry; Conducted validation of administrative claims data for medical device evaluation

2. Centers of Excellence

FDA's Centers of Excellence in Regulatory Science and Innovation (CERSI) maintain websites providing information on their research projects, training activities conducted, and scientific publications.

University of Maryland CERSI[172]
Georgetown University CERSI[173]
University of California San Francisco-Stanford CERSI[174]
Johns Hopkins University CERSI[175]
Yale University Mayo Clinic CERSI[176]

3. FDA Guidances

FDA maintains a listing of its guidances[177] that can be searched according to key words, product type, date issued, and over 100 subject areas.

4. FDA Medical Product Center Scientific Publications

FDA publications in a given time frame can be searched by author, title, Center and subject area.[178]

Scientific publications* with an author from an FDA medical product center.					
Calendar Year	CBER authorship	CDER authorship	CDRH authorship	Joint authorship	Total
2015	236	434	203	97	970
2016	248	498	220	126	1092
Total	484	932	423	223	2062

*Publications include articles, abstracts, reviews, epubs, and commentaries appearing in journals. Source – FDA Publications Database

5. FDA-sponsored Scientific Workshops

Chronological lists of science-related meetings[179] including workshops, with links to meeting information are listed according to the categories of Drugs; Vaccines, Blood, and Other Biologics; Combination Products, and General and Crosscutting Topics.

6. Examples of Training Activities Relevant to Regulatory Science

In addition to attending public scientific meetings, FDA scientists stay abreast of scientific developments by sharing information at scientific symposia, seminars, and classes at FDA. We list some major scientific

symposia, scientific training opportunities that consisted of multiple sessions rather than a single event, and ongoing seminar series.

Scientific Symposia, Seminar series, and scientific courses with multiple sessions in FY 2015 and 2016	
Scientific symposia	**No. of presentations**
CBER Science symposium	27 oral presentations., ~ 65 Poster presentations
2015 FDA Science Forum	34 presentations, >280 poster presentations
Generic Drug Science day	12 oral presentations, ~ 140 poster presentations
Recurring Seminar series*	
CDRH Neuro Lecture Series	
CDRH Science Sharing Seminars	
CDER Seminars	
Data Monitoring Committees in Industry Sponsored Clinical Trials	
DCD - Cardiac Disorders, Diagnostics and Electrophysiology	
CDRH Epidemiology Grand Rounds Program	
CBER Science Impact series	
CBER Division of Viral Products seminar series	
Regenerative Medicine Seminar Series	
CBER Office of Blood Research and Review Seminar Series	
CBER Office of Cellular, Tissue & Gene Therapies Seminar Series	
CDER Office of Biostatistics and Epidemiology Seminar Series	
CBER Division of Bacterial, Parasitic and Allergenic Products Seminar Series	
FDA Grand Rounds	
CDER Rounds	
Multi-disciplinary Office of Biostatistics-Office of Clinical Pharmacology Scientific Exchange	
CDER Office of Clinical Pharmacology Rounds	
Scientific training involving more than one session	**No. of sessions**
CDRH Statistics for Clinical Trials	11
CDRH Statistics for Diagnostic Devices	9
CDRH Introduction to Biostatistics	14
Introduction to Clinical Virology	9
General BioCompatibility Guidance Post-Test Training	2
Ophthalmic Education Series	6
CDER Office of Computational Sciences data standards training	14
CDER Office of Computational Sciences analytical tool training clinics	98
CDER Office of Computational Science Reviewer training	108
CDER OCP Introduction to Clinical Pharmacology	2 day-long sessions
Quality System Requirements and Industry Practice	2
Reprocessing Medical Devices in Health Care Settings	2
FDA Bone Seminar	2
AAMI Industrial Sterilization	5
Biocompatibility Guidance l Training	5

*These events generally occur on a monthly or bimonthly basis.

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