



May 2016

MEDICAL PRODUCT OVERSIGHT

FDA Needs More Strategic Planning to Guide Its Scientific Initiatives

Why GAO Did This Study

FDA has faced challenges regulating medical products, owing in part to rapid changes in science and technology. In 2010, FDA established a regulatory science initiative that identified eight priority areas for medical products where new research was needed to advance its mission. Legislation enacted in 2012 required FDA to establish a plan for measuring its progress on its regulatory science efforts.

GAO was asked to examine FDA's progress on its regulatory science efforts related to medical products. In this report, GAO (1) evaluates FDA's strategic planning efforts to address its regulatory science priorities, (2) describes FDA's funding targeted at regulatory science projects, and (3) describes the achievements of selected FDA regulatory science projects. GAO compared related FDA strategic planning documents to federal internal control standards and leading practices for strategic planning. GAO reviewed FDA data on obligations targeted at regulatory science projects for fiscal years 2010 through 2014 and reviewed the achievements FDA reported from a sample of 17 projects, chosen to ensure nine FDA centers and offices and priority areas are represented.

What GAO Recommends

To improve strategic planning for regulatory science efforts, FDA should (1) develop and document measurable goals, including targets and time frames, and (2) systematically track funding across its regulatory science priority areas. The Department of Health and Human Services agreed with GAO's recommendations.

View [GAO-16-432](#). For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

MEDICAL PRODUCT OVERSIGHT

FDA Needs More Strategic Planning to Guide Its Scientific Initiatives

What GAO Found

The Food and Drug Administration (FDA) lacks measurable goals to assess its progress in advancing regulatory science—the science supporting its effort to assess the products it regulates. The agency issued strategic planning documents in 2011 and 2013 to guide its regulatory science efforts and identify priority areas for conducting work, but these documents do not specify the targets and time frames necessary for the agency to measure progress overall or within each of the eight priority areas related to medical products. According to leading practices for strategic planning, identifying and using consistent measurable goals in planning and progress documents is important to assessing effectiveness. While FDA cited examples of its achievements in regulatory science in a 2015 report, FDA cannot assess how those achievements constitute progress towards its goals. In addition, FDA lacks information about how funding targeted at regulatory science is distributed across the priority areas. Decisions to award these funds are made by individual FDA centers and offices, which generally did not collect information on the associated priority areas of funded projects. Rather, FDA retrospectively identified these areas for the purpose of GAO's review. The lack of consistent information limits FDA's ability to examine obligations across, or progress within, specific priority areas. Standards for internal control in the federal government state that complete and accurate data are needed to make operating decisions and allocate resources. Furthermore, multiple centers or offices fund projects toward a given priority area and leading practices for strategic planning encourage agencies to manage efforts that cut across the agency.

FDA obligations for regulatory science projects generally increased from fiscal years 2010 through 2014 and totaled more than \$507 million across that period. Nine centers and offices obligated funds, with totals for each center or office ranging from approximately \$450,000 to about \$200 million. The Office of the Chief Scientist (in particular, the National Center for Toxicological Research) funded 65 percent of the total obligations. FDA obligated funds towards each of the regulatory science priority areas, ranging from about \$3 million for *global product safety* to approximately \$203 million for *toxicology*. The *clinical evaluations and personalized medicine* and *medical countermeasures* priority areas were also among those with the greatest obligations.

For the 17 regulatory science projects GAO reviewed, FDA identified achievements ranging from the dissemination of project findings to changes in both agency and external stakeholder practices. For example, FDA reported that all projects resulted in some type of change within FDA. About half of the projects resulted in the agency developing standards, methods, tools, or training that it could use internally, and about one-third of the projects affected guidance or regulations. FDA also reported that about half of the projects resulted in the development of new tools or standards for use by industry or other stakeholders, in areas such as setting new standards for defibrillators to account for radio interference.

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Abbreviations

CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act of 2012
GDUFA	Generic Drug User Fee Amendments of 2012
GPRA	Government Performance and Results Act of 1993
HHS	Department of Health and Human Services
NCTR	National Center for Toxicological Research
OCET	Office of Counterterrorism and Emerging Threats
OIP	Office of International Programs
OMH	Office of Minority Health
ORSI	Office of Regulatory Science and Innovation
OWH	Office of Women's Health
PDUFA	Prescription Drug User Fee Act

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May 16, 2016

The Honorable Lamar Alexander
Chairman
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Richard Burr
United States Senate

The Food and Drug Administration (FDA)—an agency within the Department of Health and Human Services (HHS)—has faced challenges carrying out its responsibilities to approve and oversee the safety and efficacy of medical products sold in the United States.¹ As a result, we identified FDA’s oversight of medical products as an area of high risk, and we noted that rapid changes in science and technology had contributed to these challenges.² However, these are not new concerns for the agency. In 2007, FDA’s Science Board reported that the agency’s ability to fulfill its mission was at risk because of a weak scientific base.³ Further, the Institute of Medicine, following a series of reports and workshops identifying gaps between the science of medical product technologies and FDA’s capacity to regulate those technologies, held a workshop in 2011 on FDA’s critical role in the area of regulatory science—which is defined by FDA as the science of developing new tools, standards, and

¹These medical products are drugs, devices, and biologic products. Biologic products—which include vaccines, blood products, and proteins—are derived from living sources such as humans, animals, and microorganisms, while drugs are chemically synthesized. Unless otherwise indicated, throughout this report we use the term “drug” to refer to both chemically synthesized drugs and therapeutic biologic products.

²GAO, *High-Risk Series: An Update*, [GAO-13-283](#) (Washington, D.C.: February 2013). See also GAO, *Prescription Drugs: FDA Has Met Most Performance Goals for Reviewing Applications*, [GAO-12-500](#) (Washington, D.C.: March 30, 2012); *Pediatric Medical Devices: Provisions Support Development, but Better Data Needed for Required Reporting*, [GAO-12-225](#) (Washington, D.C.: December 20, 2011); and *Drug Shortages: FDA’s Ability to Respond Should Be Strengthened*, [GAO-12-116](#) (Washington, D.C.: November 21, 2011).

³Food and Drug Administration Science Board, *FDA Science and Mission at Risk* (November 2007). FDA’s Science Board is comprised of non-federal experts that advise the agency on complex scientific and technical issues.

approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products.⁴ At the workshop, it was noted that regulatory science had been neglected at FDA and that the agency could take steps internally and with external partners to better keep up with new technologies and develop the expertise necessary to regulate those technologies.

To accelerate the process from scientific breakthrough to the availability of new medical products, FDA established the Advancing Regulatory Science Initiative in 2010.⁵ Since then, the agency has issued multiple documents to guide its strategic planning related to regulatory science. In 2011 and 2014, FDA named regulatory science as one of five crosscutting strategic priorities for the agency.⁶ The agency also developed a strategic plan in 2011 specifically for regulatory science that identified priority areas in which FDA would apply funding and other resources.⁷ In 2013, FDA issued another strategic plan for regulatory science, as required by the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA).⁸ This document identified regulatory science priorities with respect to FDA's decision making and included categories by which progress on the priorities would be measured. Since then, FDA issued two reports on its progress. Specifically, in May 2015, it issued a report required by FDASIA on fiscal year 2013 and 2014

⁴Institute of Medicine, *Building a National Framework for the Establishment of Regulatory Science for Drug Development: Workshop Summary* (Washington, D.C.: The National Academies Press, 2011).

⁵This initiative builds on FDA's Critical Path Initiative, which was launched in March 2004 as the agency's strategy to drive innovation in the scientific process through which medical products were developed, evaluated, and manufactured.

⁶Food and Drug Administration, *FDA Strategic Priorities: 2014-2018* (September 2014); and *FDA Strategic Priorities: 2011-2015* (April 2011).

⁷Food and Drug Administration, *Advancing Regulatory Science at FDA: A Strategic Plan* (August 2011).

⁸Pub. L. No. 112-144 § 1124, 126 Stat. 993, 1114 (2012). Food and Drug Administration, *Strategy and Implementation Plan for Advancing Regulatory Science for Medical Products* (July 2013).

activities and in July 2015, it publicly issued a report to its Science Board.⁹

Given the concerns associated with FDA's activities related to regulatory science, you requested that we provide information on whether FDA has been making progress in this area. This report

1. evaluates FDA's strategic planning efforts to address its regulatory science priorities for medical products,
2. describes FDA's funding targeted at regulatory science projects related to medical products, and
3. describes the achievements of selected FDA regulatory science projects related to medical products.

To evaluate FDA's strategic planning efforts to address its regulatory science priorities for medical products, we analyzed FDA documents, including its 2011 and 2013 strategic planning documents, its reports on strategic priorities, and a 2015 progress report. We analyzed whether the methods FDA uses to collect data and report on progress are consistent with relevant criteria identified in Standards for Internal Control in the Federal Government.¹⁰ We also reviewed relevant criteria from GAO's body of work on effectively managing performance under the Government Performance and Results Act of 1993 (GPRA) as enhanced by the GPRA Modernization Act of 2010.¹¹ We also interviewed FDA officials about how they collected information on and assessed progress within the priority areas they identified.

⁹Food and Drug Administration, *FDA Science Moving Forward: Progress Report to the FDA Science Board* (July 2015); and *FY 2013-2014 Regulatory Science Progress Report: In Fulfillment of Requirements Under the Food and Drug Administration Safety and Innovation Act, Section 1124* (Silver Spring, Md.: May 2015).

¹⁰GAO, *Standards for Internal Control in the Federal Government*, (GAO/AIMD-00-21.3.1). Internal control is a process effected by an entity's oversight body, management, and other personnel that provides reasonable assurance that the objectives of an entity will be achieved.

¹¹GAO, *Agencies' Strategic Plans Under GPRA: Key Questions to Facilitate Congressional Review*, GAO/IGD-10.1.16 (Washington, D.C.: May 1997); *Managing For Results: Key Steps and Challenges in Implementing GPRA in Science Agencies*, GAO/T-IGD/RCED-96-214 (Washington, D.C.: July 10, 1996); and *Executive Guide: Effectively Implementing the Government Performance and Results Act*, GGD-96-118 (Washington, D.C.: June 1996).

To describe FDA's funding targeted at regulatory science projects related to medical products, we analyzed available FDA data on funding for grants or other awards (referred to as "projects") targeting regulatory science from fiscal years 2010 through 2014 and interviewed FDA officials about these projects. FDA officials told us that the agency does not keep a compilation of projects that it identifies as being targeted at regulatory science. As a result, we relied on each center and office in our review to individually identify such projects for our review. We obtained data from FDA on funding obligations for these projects from FDA, examined these data for inconsistencies and sought clarification as necessary, and determined that the data were sufficiently reliable for our purposes. FDA officials indicated that the agency also funds broader efforts that benefit regulatory science along with other goals; however, these efforts were not included in our funding totals because the agency was not able to identify funding at the project level specifically for regulatory science.

To describe the achievements of selected FDA regulatory science projects related to medical products, we selected a sample of 17 projects to review, which were chosen to ensure representation of all FDA centers and offices with targeted regulatory science funding and all FDA regulatory science priority areas. First, from among those 1,279 projects that were obligated funds targeted at regulatory science from fiscal year 2010 through fiscal year 2014, we selected the project with the greatest funding during this time period for each center and office, for a total of 8 projects.¹² We excluded projects that received obligations in fiscal year 2014, as they were ongoing at the time of our selection and therefore may not have had time to demonstrate an achievement. These 8 projects represented less than 1 percent of the projects for which we had funding data, yet accounted for 5 percent of the total funding obligations for targeted regulatory science projects for fiscal years 2010 through 2013. Second, we randomly selected a sample of 9 projects from among those completed projects with achievements reported in FDA's 2014 progress report to the Science Board, ensuring representation by centers and

¹²One office obligated fiscal year 2014 funds to all of their funded projects; therefore, we did not select a project for that office.

offices and for priority areas.¹³ For each of these 17 projects, we reviewed information provided by FDA describing the results of regulatory science achievements and interviewed FDA officials. We classified these achievements into three categories: shorter-term achievements, such as sharing information via dissemination of project findings; medium-term achievements, such as internal changes at FDA; and longer-term achievements such as changes by industry and other groups outside of FDA.

We conducted this performance audit from February 2015 through May 2016 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

Background

According to FDA, the goal of its regulatory science initiative is to develop and apply the best available scientific data, knowledge, methods, and tools to reduce uncertainty and make regulatory decisions more efficient and consistent. In doing so, the agency seeks to ensure public access to products that are manufactured or processed in a high quality manner and monitored to ensure safety and quality during real-world use. FDA's 2011 strategic plan identified eight priority areas for regulatory science, of which seven related to medical products where the agency determined that new or enhanced engagement is essential to the continued success of the agency's public health and regulatory mission.¹⁴ The agency then added an additional priority area related to global product safety in 2013. (See table 1.)

¹³At the time of our selection, this document had not been published publicly. FDA subsequently published it in 2015. Food and Drug Administration, *FDA Science Moving Forward*. Three offices did not have projects listed in the progress report that were completed at the time of our review; therefore we did not select projects for those offices using that source.

¹⁴Although not part of our review, FDA also identified a priority area related to food: Implement a new prevention-focused food safety system to protect public health.

Table 1: Food and Drug Administration (FDA) Regulatory Science Priority Areas for Medical Products, as of February 2016

FDA priority area	Activities FDA describes for each priority area	Abbreviated name for FDA priority area (assigned by GAO)
Modernize toxicology to enhance product safety	Reducing gaps in understanding the relationship between patient response and preclinical toxicology findings, improving toxicology models and safety assays, advancing computational analyses	Toxicology
Stimulate innovation in clinical evaluations and personalized medicine to improve product development and patient outcomes	Translating new findings into safe and effective medical products, speeding efficacious medical products to patients, identifying biomarkers and endpoints	Clinical evaluations and personalized medicine
Support new approaches to improve product manufacturing and quality	Assessing how new technologies affect product safety, efficacy, and quality; applying novel technologies to product development	Manufacturing and quality
Ensure FDA readiness to evaluate innovative emerging technologies	Developing necessary expertise and infrastructure to evaluate new and emerging technologies	Emerging technologies
Harness diverse data through information sciences to improve health outcomes	Constructing the information technology infrastructure necessary for complex data integration	Information sciences
Facilitate development of medical countermeasures to protect against threats to U.S. and global health and security	Advancing regulatory science for medical countermeasure development and evaluation	Medical countermeasures
Strengthen social and behavioral science to help consumers and professionals make informed decisions about regulated products	Developing effective communication strategies and messages that reach diverse audiences and ensuring audience comprehension of complex information	Social and behavioral science
Strengthening the global product safety net	Advancing global public health, more effectively deploying resources against priorities, and analyzing and utilizing global data to manage risks	Global product safety

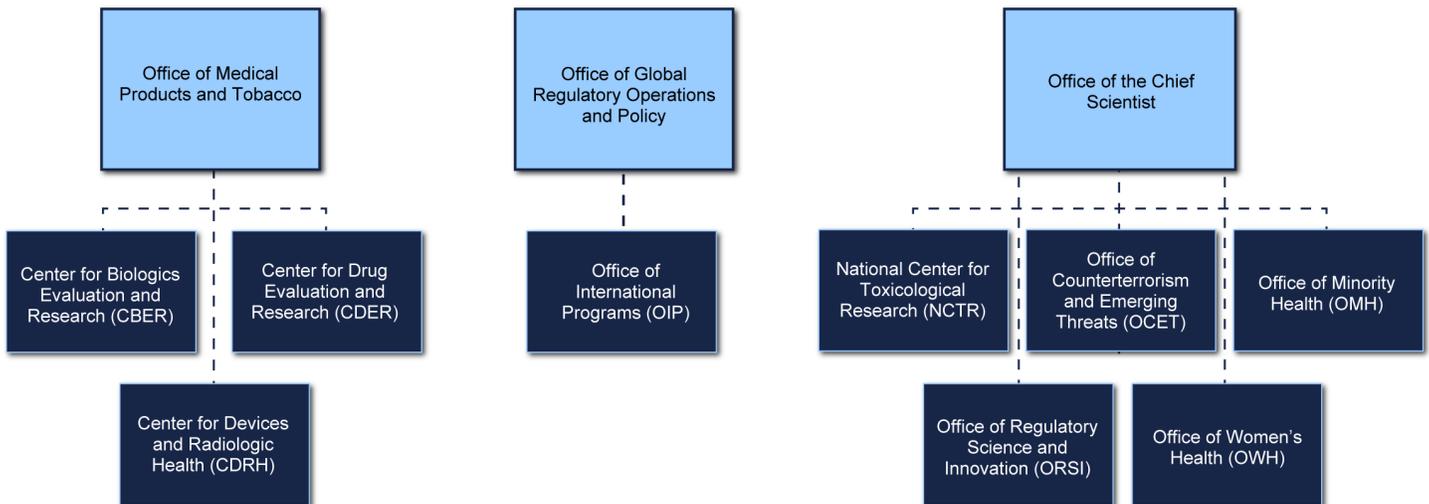
Source: GAO analysis of FDA documents. | GAO-16-432

Note: FDA also identified an additional priority area related to food safety that was not part of our review.

FDA conducts work to advance regulatory science through intramural research and extramural collaborations, such as collaboration with other government agencies, academia, industry, patient organizations, professional associations, and other stakeholders. Targeted funding for regulatory science at FDA comes from a number of centers and offices, including the Center for Biologics Evaluation and Research (CBER), the Center for Drug Evaluation and Research (CDER), and the Center for Devices and Radiologic Health (CDRH), all within FDA’s Office of Medical Products and Tobacco. These centers are responsible for approving medical products (biologics, drugs, and devices, respectively) and monitoring their ongoing safety once approved. In addition, other offices support the regulatory mission of FDA, such as the Office of International Programs (OIP) in the Office of Global Regulatory Operations and Policy, and those under the Office of the Chief Scientist—whose mission is to

provide strategic leadership, coordination and expertise—including the National Center for Toxicological Research (NCTR), the Office of Counterterrorism and Emerging Threats (OCET), the Office of Minority Health (OMH), the Office of Regulatory Science and Innovation (ORSI), and the Office of Women’s Health (OWH). (See fig. 1.) Additional broad regulatory science efforts may occur within these centers and offices as well as others at FDA.

Figure 1: Food and Drug Administration (FDA) Centers and Offices with Targeted Regulatory Science Projects Related to Medical Products, as of February 2016



Source: GAO analysis of FDA information. | GAO-16-432

FDA Lacks the Measurable Goals and Funding Information Necessary to Conduct Strategic Planning for Regulatory Science Priorities

FDA does not have measurable goals, such as targets and time frames, to assess its progress in advancing regulatory science. Further, FDA does not consistently track information on center and office funding decisions for each FDA priority area, leaving it without important information needed to conduct strategic planning on the agency's regulatory science priorities.

FDA Lacks Measurable Goals to Assess Progress Meeting Its Regulatory Science Priorities

FDA's 2011 and 2013 strategic planning documents do not identify measurable goals, such as targets and time frames, for assessing progress in regulatory science.¹⁵ For example, the 2013 strategic planning document states that FDA will measure progress by enumerating and describing product-specific advisory committees and staff training opportunities related to the priority areas. However, the document neither sets any targets or time frames, nor establishes further outcome-based measures for what FDA hopes to achieve for either a given priority area or regulatory science in general. Likewise, FDA's 2011 strategic planning document presents strategies for addressing the priority areas, but the document does not include measurable goals within these strategies.¹⁶ For example, it indicates that addressing the *toxicology* priority area would involve developing human and animal models to predict adverse responses, but it does not provide the number of models FDA intends to develop or the adverse responses for which the models

¹⁵Food and Drug Administration, *Advancing Regulatory Science at FDA: A Strategic Plan* (August 2011); and *Strategy and Implementation Plan for Advancing Regulatory Science for Medical Products* (July 2013). In addition to the strategic planning documents, FDA also has issued 2011-2015 and 2014-2018 strategic priorities documents that explain how regulatory science is an important element in achieving FDA's crosscutting work, but these broad documents do not include measurable goals for assessing progress in regulatory science.

¹⁶The 2011 FDA strategic plan does not include strategies for addressing the *global product safety* priority area because the plan was published before the priority area was established.

are intended. FDA's lack of specific measurable goals is reflected in the progress report that it completed for FDASIA.¹⁷ In that report, FDA includes examples of achievements but it does not specify overall results, such as the number of tests and technologies developed for the efficacy and safety of medical products, which the 2013 planning document indicated would help the *manufacturing and quality* priority area. In addition, FDA generally did not link the categories that it used to measure the adoption of regulatory science to a specific priority area. Specifically, in the progress report, only four of the eleven categories are linked to the FDA priority areas that they address.¹⁸ For example, while FDA reported one or more related FDA priority area for each guidance document included in the progress report, it did not provide the same information for the reported training examples or the projects included in the Drug Development Tool Qualification programs.¹⁹

According to our work on leading practices for strategic planning, an agency's strategic goals should explain what results are expected from the agency and when to expect those results.²⁰ It is also critical that the strategic planning documents describing these goals include specific actions and implementation schedules for how the agency is to achieve these goals.²¹ Without measurable goals, clear targets, and implementation time frames, FDA cannot provide a complete assessment of progress made in the regulatory science areas it has designated as priorities.

¹⁷Food and Drug Administration, *FY 2013-2014 Regulatory Science Progress Report*.

¹⁸FDA's progress report identified the FDA priority areas for these four categories: examples of achievements in advancing regulatory science, guidance documents, scientific publications, and examples of public workshops. FDA's progress report did not identify FDA priority areas for the seven remaining categories—collaborative interactions with external partners, develop and deploy systems and tools to support regulatory review, examples of consultation with international regulators, examples of FDA training, examples of regulatory action communication, number of projects in the Drug Development Tool Qualification programs, and standardization of clinical trial data.

¹⁹The Drug Development Tool Qualification programs were created by FDA to provide a framework for development and regulatory acceptance of scientific tools, such as biomarkers and animal models, for use in drug and biologic development programs.

²⁰GAO, *Agencies' Strategic Plans Under GPRA: Key Questions to Facilitate Congressional Review*, [GAO/GGD-10.1.16](#) (Washington, D.C.: May 1997).

²¹[GAO/GGD-97-180](#).

According to FDA officials, it is difficult to measure the progress made in the priority areas because the priority areas are very broad and the underlying science is continually changing. Furthermore, the adoption of discoveries from regulatory science research can take years. Because the priority areas are managed across multiple organizational units, they are not being overseen by a specific center or office. However, we have previously recognized that while measuring the performance of science-related projects can be difficult, science-related agencies like FDA should still have clearly established goals.²²

One of the centers that targets funding at regulatory science has a plan to track the progress of its regulatory science activities, but this plan does not include measurable goals that could be used to assess progress. Specifically, CDRH officials told us the center has drafted a logic model to identify and track the short- and long-term outcomes of funds it spends on regulatory science research. The center expects the model to be finalized in 2017. However, the current draft does not include measurable goals to assess progress. In addition, officials from most of the other centers and offices that obligated funds targeted at regulatory science activities in fiscal years 2010 through 2014 told us they are not developing such a model.²³ One office also stated that the CDRH model may not be applicable to their work and that they may not have the resources needed to customize and implement such a model. In another effort, FDA officials indicated that the agency recently initiated internal discussions primarily to share information, and if feasible and desired, harmonize best practices within the agency. FDA officials also said that this group would discuss evaluation strategies and processes and perhaps eventually arrive at a common FDA approach to thinking about research outcomes and impact. This group first met in October 2015 to discuss current efforts, and FDA officials reported in April 2016 that it is still in the early stages of sharing information.

²²GAO, *Results-Oriented Government: GPRA Has Established a Solid Foundation for Achieving Greater Results*, [GAO-04-38](#) (Washington, D.C.: March 2004); and [GAO/T-GGD/RCED-96-214](#).

²³CBER officials stated that in fiscal year 2017 they plan to implement a research impact framework to evaluate research productivity at the center. However, the documentation that they provided does not show that this framework is specific to regulatory science, nor does it show how short- and long-term impacts would be measured. OIP officials told us they are developing a framework to measure outcomes. However, this framework applies to OIP's work in general and is not specific to regulatory science.

FDA Lacks Information Necessary to Track Funding and Strategically Plan for Its Regulatory Science Priorities across the Agency

FDA does not have the information necessary to track funding and conduct strategic planning agency-wide for its regulatory science priorities because most of the centers and offices did not collect information on the FDA priority areas that were addressed by the projects they funded. As a result, information on funding for each priority area is generally not readily available and therefore the majority of these centers and offices had to retrospectively assign FDA priority areas to each project at the time of our review.

- Six centers and offices—CDRH, NCTR, OCET, OIP, OMH, and OWH—fund regulatory science projects that address multiple FDA priority areas, but generally did not collect information about how funds are distributed across those priority areas. All six had to retrospectively identify associated FDA priority areas for our review. For example, while CDRH and NCTR collect some information about research priorities for the projects they fund, the information they collect does not fully align with the FDA priority areas. Specifically, CDRH collects information on its own set of priorities and NCTR collects information on FDA goals. While this information is partially aligned with the FDA priority areas, there is not a one-to-one correspondence, thus information on FDA priority areas is not readily available. According to NCTR officials, they began capturing information on the FDA priority areas in 2016. Further, OMH asks researchers to identify the unmet regulatory science need that their proposed research addresses, but the researchers are not asked to identify specific FDA priority areas. In addition, OCET and OIP officials told us that all of their funded projects are related to one FDA priority area, and therefore they do not collect information about other priority areas. However, there is no guarantee they will not fund projects related to other priority areas in the future. Further, while OIP told us they focus on just the FDA priority area *global product safety*, the data they provided for our review also identified an additional priority area, *information sciences*, as an FDA priority area being addressed by some of their projects.
- Three offices, CBER, CDER, and ORSI, collect some information on the FDA priority areas addressed by their targeted projects. CBER and CDER have not collected this information at the time of funding. Rather, CBER asks researchers to provide it as part of required annual reports and CDER officials indicated that CDER has made a

similar request of researchers since 2012.²⁴ Officials from both CBER and CDER said that in the near future their centers plan to track the FDA priority areas at the time projects are proposed for funding. ORSI asks researchers to identify FDA priority areas for its broad agency announcements, which are competitive funding announcements for extramural research programs and accounted for 21 percent of ORSI's funding for the projects that we reviewed. ORSI does not ask this of researchers applying for its other regulatory science funding programs, although the announcements for the intramural grants state that the proposals should align with one or more of the eight original priority areas. For these other funding programs, ORSI confirms that a project proposal is related to regulatory science, but does not document any specific FDA priority area for that project.

While each center or office may be funding projects that are generally consistent with the priority areas that FDA established, without consistent information from each center or office detailing those connections, the agency is not able to examine obligations across specific priority areas. Standards for internal control in the federal government state that complete and accurate data are needed to make operating decisions and to allocate resources.²⁵ In addition, to ensure program goals are met, our work encourages agencies to manage efforts that cut across the agency.²⁶ Without complete information on the allocation of funding across priority areas by centers and offices, FDA cannot ensure that funding is being distributed in line with its strategic plan.²⁷

²⁴Currently, CBER and CDER ask researchers to identify all of the FDA priority areas associated with their research projects, although the *global product safety* priority area is not provided as an option.

²⁵See [GAO/AIMD-00-21.3.1](#).

²⁶[GAO/T-GGD/RCED-96-214](#).

²⁷In a previous review of FDA's activities more broadly, we reported that the agency also generally lacked clear alignment between the activities that it funds and its goals. We concluded that such alignment is a critical step in making budgetary decisions and without it Congress' ability to assess the likelihood of FDA's success is hindered. GAO, *Food and Drug Administration: Opportunities Exist to Better Address Management Challenges*, [GAO-10-279](#) (Washington, D.C.: Feb. 19, 2010).

FDA Annual Obligations for Regulatory Science Projects Generally Increased from 2010 through 2014 and Varied across Centers and Offices and Priority Areas

In response to our request, FDA identified projects targeted at regulatory science funded from fiscal years 2010 through 2014 totaling more than \$507 million. Annual obligations for these projects generally increased during that time. This funding varied across centers and offices, ranging from approximately \$450,000 to about \$200 million. In addition, while FDA does not systematically track regulatory science obligations by priority area, the agency's retrospective review showed wide funding variation across priority areas, ranging from about \$3 million to approximately \$203 million.

FDA Annual Obligations for Regulatory Science Projects Generally Increased over Time

FDA obligations targeted at regulatory science projects increased from about \$73 million in fiscal year 2010 to a peak of about \$123 million in fiscal year 2013, then a decline to about \$110 million in fiscal year 2014. These funds represent those obligations targeted at specific regulatory science projects and do not include FDA obligations for other activities benefitting regulatory science for which the agency was not able to quantify spending at a project level.²⁸ (See fig. 2.) Over the 5 years we examined, FDA obligated nearly \$507 million for 1,279 regulatory science projects, an average of approximately \$400,000 per project.²⁹ Total obligations for individual projects ranged from \$430 to \$9.1 million during this time.³⁰ While FDA obligated funds for some projects for a single year, FDA typically obligated funds for projects in multiple years.³¹

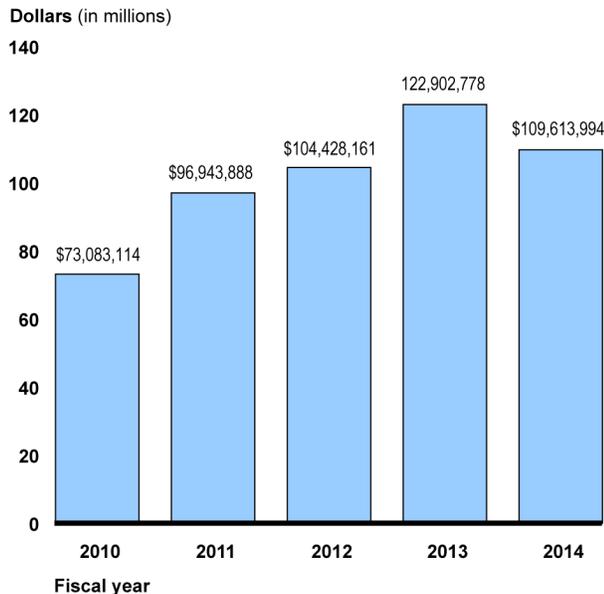
²⁸FDA reported only funding information that it could identify at the project level. In addition, FDA officials indicated that centers and offices used their own definitions to identify funding targeted at regulatory science projects. For example, some centers and offices included staffing and overhead costs in the funding they reported, while others did not.

²⁹A small number of projects were funded by more than one center or office at FDA. Those projects are counted twice in the total number of projects.

³⁰For the project that received \$430, FDA reported funding for only 2010 and we did not ask for funding from prior years.

³¹We report funding amounts based on the year in which FDA obligated the funds, which is not necessarily the year in which work was done on the project.

Figure 2: Food and Drug Administration (FDA) Obligations Targeted At Regulatory Science, Fiscal Years 2010-2014



Source: GAO analysis of FDA data. | GAO-16-432

Note: These obligations were targeted at regulatory science and do not include FDA obligations for other activities benefitting regulatory science for which the agency was not able to quantify spending at a project level.

FDA obligated 80 percent of these regulatory science funds to intramural projects—those led by FDA researchers. For example, the Office of the Chief Scientist’s grant program includes five intramural grant programs; for these programs, FDA scientists first submit concept papers that are ranked and then submit full proposals that are peer-reviewed. The remaining 20 percent of projects were either extramural or a combination of intramural and extramural. For example:

- Broad Agency Announcements are extramural, competitive funding announcements supporting regulatory science research programs.
- Centers of Excellence in Regulatory Science and Innovation are extramural partnerships between FDA and universities to promote cross-disciplinary regulatory science training and research.
- The Critical Path Initiative started in 2004 to improve medical product development, evaluation, and manufacturing and is used to support intramural research and external collaborations. Most Critical Path

Initiative projects were intramural, except for ten projects that were both intramural and extramural.

Of the total funding targeted at regulatory science projects, 48 percent was obligated for projects awarded through a non-competitive award process, 39 percent through a competitive award process, and 13 percent through a combination of competitive and non-competitive processes.

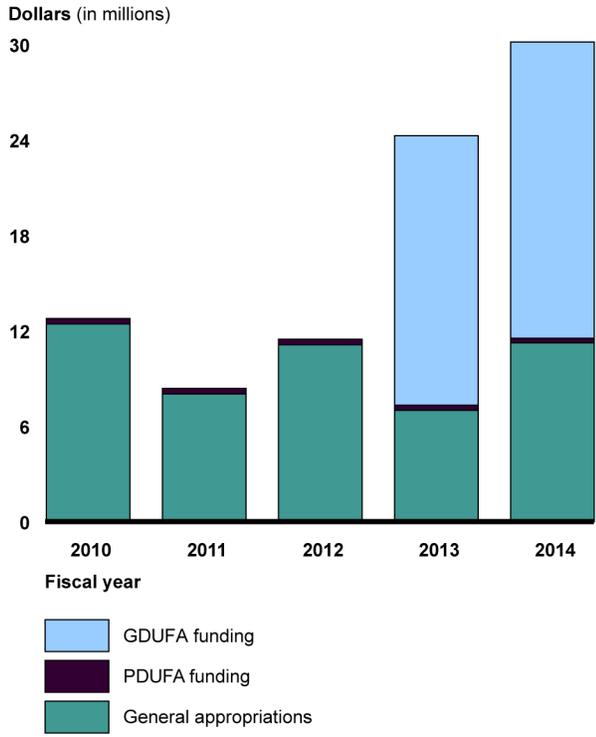
Officials reported that FDA has traditionally funded regulatory science projects with FDA general appropriations, but projects funded within CDER have also been supplemented by funds collected under user fee acts—specifically the Prescription Drug User Fee Act (PDUFA) and Generic Drug User Fee Amendments of 2012 (GDUFA)—that authorize the collection of funds from industry (including the pharmaceutical and biotechnology industries). PDUFA funds accounted for 2 percent of CDER’s total regulatory science obligations for fiscal years 2010 through 2014, ranging from 1 to 4 percent annually, with approximately \$300,000 of PDUFA funds obligated each year for regulatory science.³² Starting in fiscal year 2013, CDER committed to using a portion of its GDUFA funds for regulatory science. GDUFA funds accounted for 65 percent of CDER’s regulatory science obligations in fiscal years 2013 and 2014 combined, about \$17 million (70 percent) and \$19 million (62 percent), respectively. (See fig. 3.) In 2013, the addition of funds from GDUFA more than doubled CDER’s annual obligations for regulatory science projects for fiscal years 2010-2013.³³ GDUFA and PDUFA are the only two user fee programs that support targeted regulatory science obligations.³⁴

³²CDER officials reported that the CDER Critical Path program and other activities benefiting regulatory science also received PDUFA funding during this time period. However, CDER officials could not isolate PDUFA funding at the project level because the sources included a mixture of PDUFA funds and FDA general appropriations. Therefore, there may be additional PDUFA funds for these projects that are not captured here.

³³GDUFA was enacted in 2012, and represented the first time FDA had authority to collect user fees from generic drug manufacturers. In contrast, the agency has had authority to collect fees from manufacturers of new human drugs since 1992.

³⁴FDA is authorized to collect other user fees under the Biosimilar User Fee Act of 2012 and the Medical Device User Fee Amendments of 2012.

Figure 3: Center for Drug Evaluation and Research (CDER) Obligations Targeted at Regulatory Science Based on User Fees and General Appropriations



PDUFA—Prescription Drug User Fee Act
 GDUFA—Generic Drug User Fee Amendments of 2012

Source: GAO analysis of Food and Drug Administration (FDA) data. | GAO-16-432

Note: These obligations were targeted at regulatory science and do not include FDA obligations for other activities benefitting regulatory science for which the agency was not able to quantify spending at a project level. CDER officials reported that the CDER Critical Path program and other activities benefitting regulatory science also received PDUFA funding during this time period. However, CDER officials could not isolate PDUFA funding at the project level because the sources included a mixture of PDUFA funds and FDA general appropriations. Therefore, there may be additional PDUFA funds for these projects that are not captured here.

In addition, FDA indicated that it funded other efforts benefitting regulatory science, but was unable to quantify spending at the project level. For example, CDER officials told us that funds targeted at regulatory science identified for our review represent only a portion of CDER’s investment in regulatory science. They added that lab programs, like those in the Office of Pharmaceutical Quality and the Division of Applied Regulatory Science within the Office of Translational Sciences,

fund the bulk of their projects through the normal CDER budgeting process and therefore are not included among the targeted funds.³⁵ One such CDER project focused on developing an analytical method that sponsors could use to support that proposed generic and brand name forms of estrogen are chemically equivalent. The work resulted in new recommendations for some estrogen analyses, which were incorporated into a guidance document for the development of generic estrogen products.³⁶

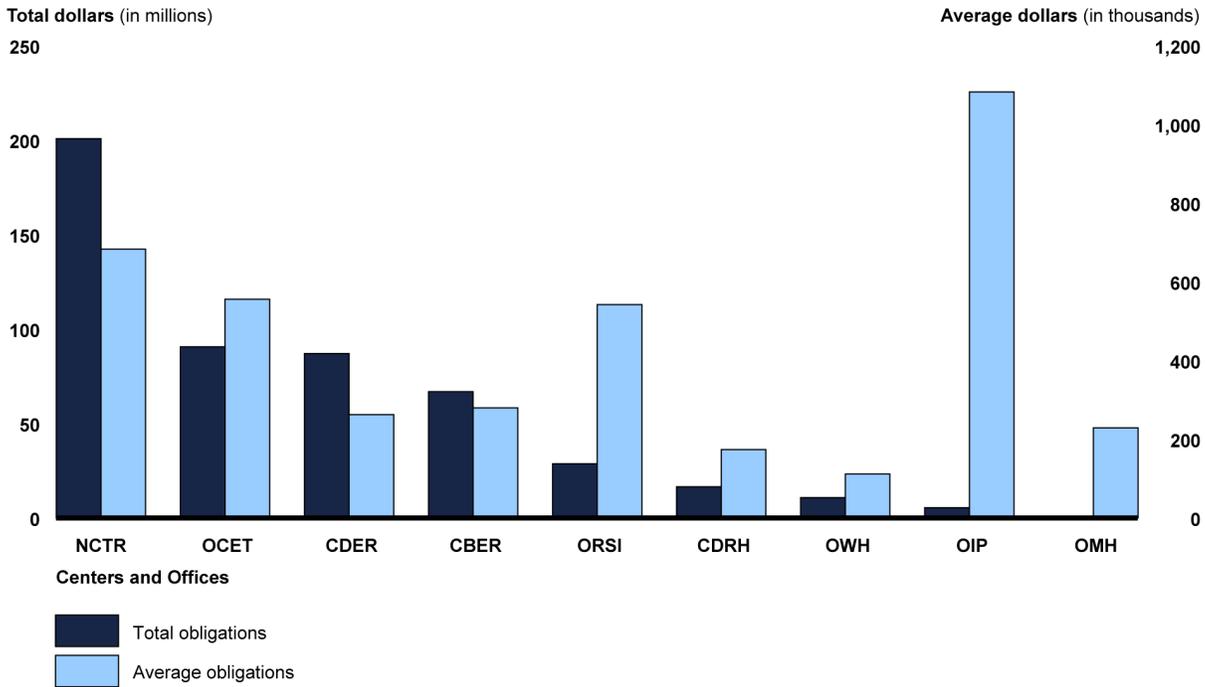
FDA Obligations for Regulatory Science Varied Widely across Centers and Offices and Priority Areas

Of the nine centers and offices that obligated funds targeted at regulatory science from fiscal year 2010 through fiscal year 2014, total obligations ranged from approximately \$450,000 by OMH to about \$200 million by NCTR. The center and offices within the Office of the Chief Scientist—NCTR, OCET, OMH, ORSI, and OWH—accounted for 65 percent of FDA’s total obligations for projects targeted at regulatory science, with NCTR accounting for 60 percent of the total Office of the Chief Scientist’s obligations. Centers with regulatory responsibilities for medical products (CDER, CBER, and CDRH) accounted for 34 percent of the obligations, and OIP accounted for the remaining 1 percent. The average obligation per project by centers and offices ranged from just over \$110,000 for OWH to about \$1.1 million for OIP. However, the centers and offices that had the highest total obligations were not necessarily the ones that had the highest average obligation at the project level. For instance, OIP had the highest average obligations per project, more than \$1 million, yet it had the second lowest total obligations, at about \$5.4 million. (See fig. 4.)

³⁵The Office of Pharmaceutical Quality is organized to streamline regulatory research and enhance understanding, assessment, and surveillance of drug quality in an effort to modernize the regulation of pharmaceutical manufacturing and enhance product quality. The Division of Applied Regulatory Science was established in September 2013 to develop laboratory data, data-based tools, best practices, and approaches to address immediate and emerging regulatory science issues that impact the development, evaluation, and utilization of new therapeutic products.

³⁶Food and Drug Administration, *Draft Guidance on Conjugated Estrogens* (December 2014).

Figure 4: Food and Drug Administration (FDA) Total Obligations and Average Obligation per Project Targeted at Regulatory Science by Centers and Offices, Fiscal Years 2010-2014



CBER—Center for Biologics Evaluation and Research
 CDER—Center for Drug Evaluation and Research
 CDRH—Center for Devices and Radiological Health
 NCTR—National Center for Toxicological Research
 OCET—Office of Counterterrorism and Emerging Threats
 OIP—Office of International Programs
 OMH—Office of Minority Health
 ORSI—Office of Regulatory Science and Innovation
 OWH—Office of Women’s Health

Source: GAO analysis of FDA data. | GAO-16-432

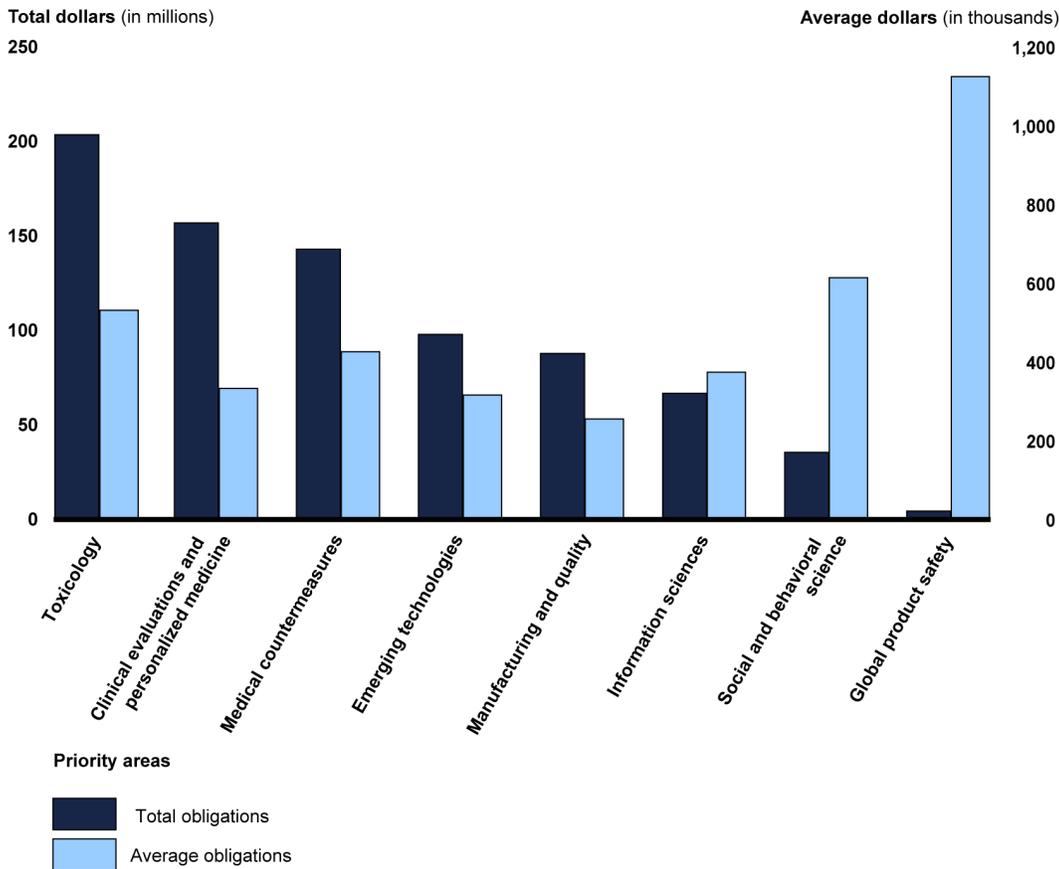
Note: These obligations were targeted at regulatory science and do not include FDA obligations for other activities benefitting regulatory science for which the agency was not able to quantify spending at a project level. FDA officials indicated that centers and offices used their own definitions to identify funding targeted at regulatory science projects. Data from CBER included some obligations that grouped multiple projects. For these, we were not able to identify individual project counts and therefore counted each grouping as a single project. As a result, the average obligations per project for CBER may be overstated.

Similarly, total obligations associated with each FDA regulatory science priority area varied widely, ranging from about \$3 million for projects that focused on *global product safety* to approximately \$203 million for

projects that focused on the *toxicology* priority area.³⁷ (See fig. 5.) Projects that focused on the *clinical evaluations and personalized medicine* and *medical countermeasures* priority areas were among those with the greatest obligations. Average obligations per project ranged from about \$250,000 for the projects that focused on the *manufacturing and quality* priority area to approximately \$1.1 million for the projects that focused on the *global product safety* priority area. However, the FDA priority areas that had the lowest total obligations were not necessarily the ones that had the lowest average obligation at the project level. For example, projects that included a focus on *global product safety* had the lowest total obligations but they had the highest average obligation per project. Similarly, projects that included a focus on *social and behavioral science* had the second lowest total obligations but they had the second highest average obligation per project.

³⁷A majority of FDA officials retrospectively assigned priority areas for each of the projects in our review. FDA identified multiple priority areas for some projects and indicated that these could not be prioritized. Therefore, for a given project, we counted the full amount of the obligations for each priority area identified for that project.

Figure 5: Food and Drug Administration (FDA) Total Obligations and Average Obligation per Project Targeted at Regulatory Science by Priority Area, Fiscal Years 2010-2014



Source: GAO analysis of FDA data. | GAO-16-432

Note: FDA identified multiple priority areas for some projects and indicated that these could not be prioritized. Therefore, the full amount of the obligations for each priority area identified for each project are counted and thus the total obligations across the priority areas exceed FDA's total obligations for regulatory science. The obligations in this figure were those targeted at regulatory science and do not include FDA obligations for other activities benefitting regulatory science for which the agency was not able to quantify spending at a project level.

FDA's centers and offices make decisions about funding that determine which projects to fund, and they generally obligated project funds across several regulatory science priority areas. Specifically, two-thirds of the centers and offices provided obligations to five or more priority areas. For example, CBER provided obligations to projects that collectively focused on every priority area except *global product safety*. Nevertheless, there were four centers and offices that directed at least half of their regulatory science obligations to a single priority area.

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- 100 percent of OCET obligations were for *medical countermeasures*.
 - 62 percent of OIP obligations were for *global product safety*.
 - 56 percent of NCTR obligations were for *toxicology*.
 - 50 percent of OWH obligations were for *clinical evaluations and personalized medicine*.

While funding for each of the FDA priority areas generally came from a number of different centers and offices, for all but two priority areas, there was one center or office that accounted for the majority of obligations.

- *Global product safety*: 100 percent of the obligations from OIP.
- *Toxicology*: 82 percent of the obligations from NCTR.
- *Social and behavioral science*: 76 percent of the obligations from CDER.
- *Medical countermeasures*: 64 percent of the obligations from OCET.
- *Manufacturing and quality*: 56 percent of the obligations from CBER.
- *Emerging technologies*: 55 percent of the obligations from CBER.
- *Information sciences*: 49 percent of the obligations from NCTR.
- *Clinical evaluations and personalized medicine*: 43 percent of the obligations from NCTR.

FDA Reported That the Selected Regulatory Science Projects Led to Changes in Agency and External Stakeholder Practices

FDA reported that the 17 regulatory science projects that we selected for review helped to advance regulatory science. (See appendix I for additional information about each of these 17 projects.) For each of these 17 projects, FDA identified achievements that we classified as dissemination of project findings, internal changes at FDA, and changes by industry and groups outside of FDA. (See fig. 6.)

Figure 6: GAO Categorization of Achievements Reported by the Food and Drug Administration (FDA) for 17 Selected Regulatory Science Projects

Project name (Center/Office)	Dissemination of project findings				Internal impacts					External impacts	
	Scientific publications	Public or external conferences, presentations or symposiums	Internal FDA workshops or other events	Other mechanisms	Highlighted information that FDA is using or considering using	Additional studies or activities planned or conducted by FDA	Development of standards, methods, tools, models, or training for use by FDA	Issuance (or decision not to issue) or revision of guidance or regulations	Changes to FDA's review process	Development of tools or proposed standards for use by industry	Implementation or use of new tools or standards by industry or outside organizations
Stem Cell Quality (CBER)	■	■	■	■	■	■			■	■	■
Smallpox Vaccines (CBER)	■	■	■		■	■	■				
Influenza Vaccine Immunity (CBER)	■	■	■		■	■	■		■	■	■
Surrogate Endpoints (CDER)	■	■					■				
Advertising (CDER)	■	■	■	■	■		■				
Prescription Information (CDER)	■	■			■						
Total Disc Replacement (CDRH)	■	■			■			■	■	■	■
Connectors (CDRH)	■	■	■		■		■	■	■	■	■
Defibrillators (CDRH)	■						■		■		
Bisphenol A (NCTR)	■	■	■		■		■				■
Liver Toxicity (NCTR)	■	■	■	■		■	■		■		
Electronic Health Records (OCET)			■	■	■						
Sentinel Medical Countermeasures Surveillance (OCET)	■	■	■	■	■	■	■				
Fraudulent Products (OIP)					■	■	■				
Social Media (ORSI)	■	■				■					
Biomarkers (ORSI)			■			■			■	■	
Degrading Device (OWH)	■	■	■		■	■	■	■	■	■	

CBER—Center for Biologics Evaluation and Research
 CDER—Center for Drug Evaluation and Research
 CDRH—Center for Devices and Radiological Health
 NCTR—National Center for Toxicological Research
 OCET—Office of Counterterrorism and Emerging Threats
 OIP—Office of International Programs
 OMH—Office of Minority Health
 ORSI—Office of Regulatory Science and Innovation
 OWH—Office of Women’s Health

Source: GAO analysis of FDA information. | GAO-16-432

Dissemination of project findings. For 16 of the 17 selected projects, FDA reported that it disseminated the project results in scientific publications, conferences, FDA workshops, or some combination of all three. Such dissemination provides FDA an opportunity to share new information and understanding internally and with the larger scientific community and may contribute to future regulatory science activities.

Internal impacts. FDA described internal impacts resulting from each of the 17 selected projects, many of which related to advancing FDA's scientific understanding in a particular area.

- For 12 selected projects, FDA reported that the projects resulted in new information about the topic that FDA was using or considering using for future work. For example, one goal of OCET's project looking at the feasibility of using electronic health records in public health emergencies was advancing FDA's understanding of the possibilities and limitations of using electronic health data. The findings from this project indicated that structured data in electronic health records could help the agency assess the risk of adverse events, particularly those that are severe. However, the results also indicated that this near real-time data still had some built-in delays and that the data search process cannot be fully automated. This provided FDA with information it can use as it considers using electronic health records in emergency situations.
- For 9 selected projects, FDA reported that the results led the agency to plan or conduct additional studies or activities that represent the logical next step in the particular area being studied. For example, initial results from an ORSI study of the use of social media to provide early signals of drug safety concerns showed a relationship between data obtained from social media and from FDA's adverse event reporting system.³⁸ Using that information, FDA then conducted a retrospective study for 10 safety concerns to see if there was evidence of those adverse events in social media before FDA became aware of them. FDA has since reported that the analysis identified specific limitations of the tool FDA uses in monitoring safety concerns.

Other internal impacts were related to changes in agency practices.

³⁸The FDA Adverse Event Reporting System is a database that contains information on adverse event and medication error reports submitted to FDA. FDA uses it to look for new safety concerns that might be related to a marketed product.

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- For 8 selected projects, FDA reported that the results led to the development of standards, methods, tools, or training for FDA internal use. For example, an OIP project was designed to create a tool to help secure global supply chains against the infiltration of counterfeit or substandard products. The project resulted in the production of a “roadmap” that FDA could use to develop such a system.
 - For 5 selected projects, FDA reported that the results led to either a change in guidance or regulation or the decision to not make a previously proposed change. For example, CDER funded a study of surrogate endpoints that could speed the development of new therapies for breast cancer. FDA used results from this study to inform its development of guidance to industry that described study designs in which a surrogate endpoint may be accepted by FDA as reasonably likely to predict the clinical benefit of a drug.³⁹ In response to a statutory requirement, CDER also examined whether quantitative information could be added to drug advertising to maximize consumer and health care professional understanding of the benefits and risks of the drug.⁴⁰ Based on the results of the study, the Secretary of HHS concluded that quantitative information cannot be readily applied to many drugs and therefore it is not appropriate to issue regulations that would require such information to be added to promotional labeling or advertising.
 - For 5 selected projects, FDA reported that the results led the agency to change aspects of its review process. For example, a CBER study designed to improve influenza vaccine efficacy provided information to FDA that has helped in the review of preclinical animal studies that are included in some drug applications. The study also resulted in FDA offering training for its lab members in an approach to vaccine testing that FDA says is a common part of a product review. In addition, an NCTR project developed a knowledge base about liver toxicity and has used that to advise CDER reviewers about drug-induced liver injury risk for products they were reviewing.

³⁹Food and Drug Administration, *Guidance for Industry: Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval* (Silver Spring, Md.: October 2014). A surrogate endpoint is one in which a laboratory measurement, radiographic image, physical sign, or other outcome can predict, but is not itself a measure of, real benefit.

⁴⁰Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 3507, 124 Stat. 119, 530 (2010).

External impacts. FDA described external impacts for 8 of the 17 selected projects. These projects resulted in the development of tools or proposed standards for use by industry or the implementation or use of new tools or standards by industry or outside organizations. According to FDA, it can take several years for funded research to result in these types of tools.

- For 7 selected projects, FDA reported that the results led to the development of tools or proposed standards for use by industry. For example, a CDRH study of radio interference with automated external defibrillators led FDA to recommend to an international commission that standards for these types of defibrillators be modified to account for radio interference. Similarly, FDA officials reported that results from a study funded by OWH looking at degradation of absorbable polymers used in some cardiac stents have provided guidance for industry on the design, manufacturing, and regulation of these absorbable stents.⁴¹
- For 6 selected projects, FDA reported that industry or outside organizations have made changes based on the results of these FDA-funded projects. For example, FDA told us NCTR's studies of Bisphenol A, a chemical found in certain plastics, helped FDA and the European Food Safety Authority, resolve public safety concerns. Similarly, CDRH's study of total disc replacement devices for the spine led to the development of a test guide published through the American Society of Testing and Materials International that is used by multiple manufacturers. FDA told us that the results from these tests were then part of the manufacturers' submissions for approval of these devices.

Conclusions

For several years, FDA has been aware of the need to improve its scientific base and has established multiple regulatory science initiatives, as well as prioritized areas to address that need. FDA projects targeted at advancing regulatory science have led to internal and external impacts in understanding new science associated with medical products. However, the agency has not identified measurable goals in their strategic plans or reports on strategic priorities, such as specific targets and time frames, for regulatory science. Such goals are a best practice for strategic

⁴¹An absorbable polymer is a chemical compound that is used in implantable devices that eventually dissolve and are absorbed into the body.

planning and could enable FDA to assess and report its progress in addressing its identified priority areas and strategically plan and allocate resources for its broader regulatory science initiative. The agency faces another obstacle to its strategic plan without consistent information about centers and offices' distribution of targeted regulatory science funding among those identified priority areas. The individual centers and offices that decide which projects to fund are either tracking the priority areas in different ways or not all. Our prior work encourages the proactive collection of consistent information and standards for internal control recommend federal agencies have complete and accurate data for making funding decisions. Systematic tracking by each center or office is needed for the agency to examine obligations across, or progress within, specific priority areas and would help the agency to strategically plan for its regulatory science initiative as a whole.

Recommendations for Executive Action

In order to improve FDA's strategic planning for regulatory science efforts, we recommend the Secretary of Health and Human Services direct the Commissioner of FDA to take the following two actions:

1. Develop and document measurable goals, such as targets and time frames, for its regulatory science efforts so it can consistently assess and report on the agency's progress in regulatory science efforts.
2. Systematically track funding of regulatory science projects across each of its priority areas.

Agency Comments and Our Evaluation

We provided a draft of this report to HHS. HHS concurred with our recommendations and provided written comments, which are reprinted in appendix II. In its written comments, HHS agreed with the importance of strategic planning for regulatory science. HHS concurred with our recommendation that FDA should develop and document measurable goals; HHS suggested that agency documents with a targeted focus, such as user fee commitment letters and specific planning documents, are a more appropriate place for such goals than an agency-level strategic plan. In our recommendation to HHS, we do not specify where such goals should be documented. We recognize, as HHS noted in its comments, that advancing regulatory science is an uncertain and non-linear path that can make it challenging to set targets for specific accomplishments. Nevertheless, FDA should develop measureable goals that are related to the impacts that are discussed in HHS's comments, including the effectiveness and efficiency of FDA's regulatory review, new pathways for medical product development, enhancements in the

agency's ability to provide useful guidance to sponsors, and new technologies to monitor manufacturing and real world use of approved medical products. As all but one of the agency-wide priority areas are being addressed by projects funded by multiple centers and offices, it is important that FDA develop and document measurable goals that encompass the efforts of multiple centers and offices. HHS also concurred with our recommendation to systematically track funding across FDA's regulatory science priority areas, and the department identified recent and planned activities of specific centers to improve such tracking. We support these efforts and reiterate the importance of FDA systematically track funds agency-wide for each of the priority areas it developed. Systematic tracking of both progress on measurable goals and funding is essential for FDA to strategically plan its regulatory science initiative across the agency. In addition to these general comments, HHS provided technical comments, which we incorporated as appropriate.

As agreed with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution until 30 days from the report date. At that time, we will send copies to the Secretary of Health and Human Services and other interested parties. In addition, the report is available at no charge on the GAO website at <http://www.gao.gov>. If you or your staff have any questions about this report, please contact me at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made key contributions to this report are listed in appendix III.



Marcia Crosse
Director, Health Care

Appendix I: Description of Projects Included in Our Review of Achievements Resulting from FDA's Regulatory Science Projects

We examined the achievements related to regulatory science for 17 projects funded by the Food and Drug Administration (FDA). Below is a brief description of each project, including examples of achievements resulting from that project, according to information provided by FDA.

Stem Cell Quality

Title: Created new approaches to identify and understand critical product quality attributes of complex products, such as stem cell-derived products (both animal and human) and complex systems of medical devices.

Center or office funding project: Center for Biologics Evaluation and Research (CBER)

Priority area(s) covered: *Emerging technologies and medical countermeasures*

Funding obligations and time period of funding: \$4.513 million (fiscal years 2010 through 2014)

Description of project: Certain stem cells are being used in clinical trials for multiple medical conditions. However, multiple factors, including donor variation and culture conditions may affect the clinical performance of the stem cells either in terms of safety, efficacy, or both. This project was designed to identify product attributes that correlate with specific outcomes and to increase understanding of factors that might affect stem cell-derived safety and efficacy. This project also included the development of methods to quantify various attributes of these cells.

Select achievements reported by FDA: The project's findings affected FDA reviewers' understanding of stem-cell products. Further, the findings have helped producers of stem cell products with their studies, specifically noting that some sponsors have adopted quantitative methods for assessing the stem cells. The findings were important in the scientific reasoning in two guidance documents. Additional projects have been planned to further advance understanding in this area.

Smallpox Vaccines

Title: Developing new approaches for measuring the quality of next-generation smallpox vaccines.

Center or office funding project: CBER

Priority area(s) covered: *Medical countermeasures*

Funding obligations and time period of funding: \$0.537 million (fiscal years 2010 through 2014)

Description of project: The goal of the project was to evaluate factors that affect the safety and efficacy of smallpox vaccines and to develop new methods to evaluate smallpox vaccine quality—specifically, potency. The studies were aimed at helping the development of new smallpox vaccines.

Select achievements reported by FDA: Results from the project informed FDA's understanding of various characteristics of the vaccine, as well as factors that influenced immune responses to the vaccine. FDA also reported that one of the two alternative approaches for evaluating the potency of smallpox vaccines used in clinical trials was considerably faster than traditional methods and could be adapted for future use. In addition, further studies are ongoing in other tests related to smallpox vaccines.

Influenza Vaccine Immunity

Title: Correlates of protective immunity against influenza.

Center or office funding project: CBER

Priority area(s) covered: *Manufacturing and quality, emerging technologies, and medical countermeasures*

Funding obligations and time period of funding: \$1.209 million (fiscal years 2010 and 2011)

Description of project: This project was designed to support the development of seasonal and pandemic influenza vaccines by identifying mechanisms that contribute to immunity and developing measures of those responses.

Select achievements reported by FDA: This project resulted in the development of a new method that was useful for testing influenza vaccines, the discovery of certain characteristics that are important for producing protective immunity, and the determination of the amount of a vaccine ingredient that is needed to produce immunity. FDA reported that the project provided a foundation for training lab members in development and validation of an approach to vaccine testing, while also providing the basis for an international study led by CBER to assess reproducibility in one of the methods developed in this project.

Surrogate Endpoints

Title: Evaluating a surrogate endpoint that could speed development of new therapies for breast cancer.

Center or office funding project: Center for Drug Evaluation and Research (CDER)

Priority area(s) covered: *Clinical evaluations and personalized medicine*

Funding obligations and time period of funding: FDA could not determine funding as the research was conducted as part of FDA employees' regular responsibilities.

Description of project: FDA conducted research to assess and evaluate the validity and potential applications of a surrogate endpoint—a measure that can predict, but is not itself a measure of, benefit—in trials of treatments for women with breast cancer. By collaborating with an international working group, FDA researchers were able to use data from more than 12,000 patients.

Select achievements reported by FDA: FDA reported that researchers found a potential relationship between the surrogate endpoint and survival. This then provided important information to

drug developers for the design of future drug trials. It also informed the development of guidance to industry.¹

Advertising

Title: Completed three studies and a literature review assessing whether quantitative information could be successfully added to television and print advertisements to maximize audience understanding of benefit information in the piece, including the type of benefit information, different combinations of statistical format, and different graphic representations.

Center or office funding project: CDER

Priority area(s) covered: *Social and behavioral science*

Funding obligations and time period of funding: \$0.270 million (fiscal year 2010)

Description of project: This project was composed of four studies designed to investigate whether quantitative information in direct-to-consumer advertisements is helpful for consumers. FDA was asked by Congress to investigate this topic to determine whether such information about the benefits and risks of prescriptions drugs in a standardized format would improve health care decision-making by clinicians, patients, and consumers.

Select achievements reported by FDA: FDA reported that, based on these studies and other efforts, the inclusion of certain types of quantitative information can be helpful in some limited circumstances, but a standardized format cannot be readily applied to many drugs. It was therefore not appropriate to issue new regulations that would require such information on promotional labeling or print advertising. The findings have been used internally by an FDA working group that

¹Food and Drug Administration, *Guidance for Industry: Pathological Complete Responses in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval* (Silver Spring, Md.: October 2014), accessed February 23, 2016, <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm305501.pdf>

explores direct-to-consumer advertising. FDA reported that the findings have also been used by the external research community.

Prescription Information

Title: Experimental study of patient information prototypes.

Center or office funding project: CDER

Priority area(s) covered: *Social and behavioral science*

Funding obligations and time period of funding: \$1.613 million (fiscal year 2010)

Description of project: This project examined different methods of presenting prescription drug information to patients who obtained a prescription. The study was designed to compare the format in which information is presented, the inclusion of additional context or not, and the order of information about warnings versus information about the efficacy of the drug.

Select achievements reported by FDA: The study provided information about patient preferences for and increased comprehension of single page prototypes over the currently available format. These findings have informed FDA's development of the Patient Medication Information Initiative, which will consider a new regulation to require all prescription drugs to have a single document standardized in content and format that provides prescription information to patients in an accurate, easily understood, and balanced form.

Total Disc Replacement

Title: Development and validation of a standard test method to assess for impingement of artificial total disc replacement devices in order to provide scientific basis for regulatory guidance and better predict which devices will be clinically successful.

Center or office funding project: Center for Devices and Radiological Health (CDRH)

Priority area(s) covered: *Clinical evaluations and personalized medicine and emerging technologies*

Funding obligations and time period of funding: \$0.753 million
(fiscal years 2010 through 2012)

Description of project: The primary goal of the project was to develop a new scientific tool to characterize impingement—unintended contact between surfaces of the device—of total disc replacement devices. Impingement can be linked to premature mechanical device failure and was not accounted for in preclinical test methods. As a result, bench testing was not accurately mimicking wear and damage that was being observed clinically.

Select achievements reported by FDA: The project resulted in the development of an impingement test guide published through a professional association. As a result, multiple device manufacturers used the guide to perform impingement testing and FDA incorporated those results into their decision making on premarket approval applications and investigational device exemption submissions.

Connectors

Title: Developed standards to reduce the risk of misconnection between different types of small-bore connectors used for intravenous, feeding, neural, blood pressure cuff, and breathing system tubes to prevent serious adverse events.

Center or office funding project: CDRH

Priority area(s) covered: *Manufacturing and quality*

Funding obligations and time period of funding: FDA could not determine funding as the research was conducted as part of FDA employees' regular responsibilities.

Description of project: Because devices using small bore connectors have been accidentally connected with devices that have different functions and have led to serious adverse events for patients, including deaths, FDA participated in international efforts to standardize connector designs for specific medical applications such that they cannot be interconnected with a device for another medical application.

Select achievements reported by FDA: FDA has issued guidance on premarket recommendations for devices that use small-bore

connectors intended for use in the gastrointestinal tract. International standards are also being finalized based on this work. Device manufacturers are modifying their devices accordingly. In addition, FDA has developed a website for highlighting relevant information for stakeholders.

Defibrillators

Title: Created a general testing protocol and test methods for electromagnetic compatibility of automated external defibrillators.

Center or office funding project: CDRH

Priority area(s) covered: *Emerging technologies*

Funding obligations and time period of funding: FDA could not determine funding as the research was conducted as part of FDA employees' regular responsibilities.

Description of project: A growing number of adverse events and voluntary recalls by manufacturers of automated external defibrillators led FDA to study the effect of electromagnetic interference that had been related to potentially life-threatening failures of this device.

Select achievements reported by FDA: As a result of this project, FDA developed test methods to evaluate the susceptibility of automated external defibrillators to radiofrequency interference. FDA recommended an international commission's standards be modified to account for interference testing at certain frequencies.

Bisphenol A

Title: Physiologically based pharmacokinetic models for Bisphenol A.

Center or office funding project: National Center for Toxicological Research (NCTR)

Priority area(s) covered: *Toxicology*

Funding obligations and time period of funding: \$1.049 million (fiscal years 2010 through 2014)

Description of project: Due to concerns about the safety of Bisphenol A, which is used in many consumer plastic products, NCTR developed computational modeling to simulate infant exposure to Bisphenol A to provide FDA with information necessary to complete a safety assessment.

Select achievements reported by FDA: The results of the project allowed FDA to predict how much chemical remained after being metabolized and would get into the circulatory system of adults and infants. These models were incorporated into FDA's updated assessment on Bisphenol A and allowed FDA's Center for Food Safety and Nutrition, as well as other regulatory bodies, to determine that current uses of Bisphenol A are safe for infants and adults and, further, led the agency to conclude that the traditional safety assessment methods used were overly conservative.

Liver Toxicity

Title: Development of liver toxicity knowledge base to empower the FDA review process.

Center or office funding project: NCTR

Priority area(s) covered: *Toxicology and information sciences*

Funding obligations and time period of funding: \$3.426 million (fiscal years 2010 through 2013)

Description of project: Drug-induced liver injury is a serious safety concern that is a frequent cause of denied approvals and "black box" warnings on drugs. As a result, FDA was interested in developing a database to improve its understanding and prediction of such liver injury.

Select achievements reported by FDA: The project has produced a centralized resource of data and predictive models that are useful for both research and regulation. NCTR has trained CDER reviewers to effectively use the software from this database. NCTR also has received requests from CDER for five consultations to assess the risk of products that it has reviewed and to incorporate the software into training for new reviewers. An extension of the project is also currently under review.

Electronic Health Records

Title: Assessing the feasibility of using electronic health record systems to conduct near real-time monitoring of health outcomes, including serious or unexpected adverse events associated with medical countermeasures used during public health emergencies.

Center or office funding project: Office of Counterterrorism and Emerging Threats (OCET)

Priority area(s) covered: *Medical countermeasures*

Funding obligations and time period of funding: \$1.419 million (fiscal year 2013)

Description of project: The project was designed as a proof-of-concept feasibility study to learn whether it is possible to extract adverse event data from electronic health records and, if so, whether those data would provide useful information about the safety and effectiveness of medical countermeasures during a public health emergency.

Select achievements reported by FDA: FDA learned that electronic health records data could help inform a risk assessment of medical countermeasures based on adverse events; however, there are limits to what can be done. For example, they found it was feasible to detect severe adverse events, but that less severe adverse events were likely to be underreported.

Sentinel Medical Countermeasures Surveillance

Title: Sentinel initiative for surveillance of drugs, vaccines, and blood products used to prevent and treat pandemic influenza.

Center or office funding project: OCET

Priority area(s) covered: *Medical countermeasures*

Funding obligations and time period of funding: \$9.1 million (fiscal year 2011)

Description of project: Sentinel is FDA's system for conducting near real-time active safety surveillance of FDA-regulated medical products

through routinely collected electronic healthcare data. This project was designed to expand those capabilities to include preparedness for safety surveillance in response to the use of medical countermeasures, including for pandemic influenza.

Select achievements reported by FDA: This project created the capability for FDA to monitor the safety of medical countermeasures—for example, influenza vaccines used during an emergency, such as a pandemic. It also increased the efficiency of linkages between registries of immunization and the Sentinel database, which FDA says is vital during pandemics.

Fraudulent Products

Title: Collecting spectral information of foods, pharmaceutical ingredients, and formulated product (as well as its packaging materials) to establish a comprehensive spectral library accessible through the internet.

Center or office funding project: Office of International Programs (OIP)

Priority area(s) covered: *Information sciences*

Funding obligations and time period of funding: \$0.314 million (fiscal year 2013)

Description of project: The primary goal of this project was to develop a roadmap for the development of a global library that could potentially be used to protect consumers against fraudulent and adulterated products.

Select achievements reported by FDA: A roadmap was produced from this project and FDA intends to use it in discussions with domestic and foreign stakeholders, including other regulatory agencies and manufacturers.

Social Media

Title: Explored the potential for mining social media and other web sources to detect adverse event and safety signals.

Center or office funding project: Office of Regulatory Science and Innovation (ORSI)

Priority area(s) covered: *Information sciences*

Funding obligations and time period of funding: \$0.801 million (fiscal years 2012 through 2014)

Description of project: This study evaluated the validity and trustworthiness of using a social media data mining tool to detect drug safety events. It was also designed to evaluate the potential of social media data to provide early signals for drug safety events in postmarketing surveillance and to better understand how these data can be used.

Select achievements reported by FDA: FDA initially reported that the data mining tool suggested that user-generated data sources may identify signals not found in the traditional voluntary reporting systems and that there was agreement between data obtained from this tool and that obtained from the FDA Adverse Events Reporting System. FDA conducted an additional study to evaluate if there was evidence in social media for 10 recent MedWatch Safety Alerts prior to FDA becoming aware of them. FDA has since reported that monitoring social media did not provide early safety concerns for the medical products that were monitored in the study. The analysis identified specific limitations of FDA's tool that was used in monitoring safety concerns. These limitations related to the natural variability of data sources and the difficulties in conducting accurate evaluation of the data. FDA noted that as monitoring social media for safety concerns is a new approach, the agency still needs to establish best practices in order to use it effectively.

Biomarkers

Title: Consortium for tuberculosis biomarkers.

Center or office funding project: ORSI

Priority area(s) covered: *Clinical evaluations and personalized medicine*

Funding obligations and time period of funding: \$1.425 million (fiscal years 2010 through 2012)

Description of project: This project had three main objectives: 1) create protocols, processes, and standards by which a consortium for tuberculosis biomarkers—composed of three organizations central to tuberculosis clinical drug development—would operate; 2) create a repository for receiving, storing, and shipping samples to designated investigators; and 3) establish a peer review panel to review proposals related to the discovery and qualification of tuberculosis biomarkers, especially some surrogate markers.

Select achievements reported by FDA: The consortium established protocols for key data elements to be gathered; a consensus set of operating procedures for sample collection, processing, and storage; and quality assurance and monitoring for these activities. The consortium also adopted a peer review process to review applications for access to samples.

Degrading Device

Title: Sex-based differences in the molecular mechanisms of polymer degradation in drug eluting stents.

Center or office funding project: Office of Women's Health (OWH)

Priority area(s) covered: *Clinical evaluations and personalized medicine* and manufacturing and quality

Funding obligations and time period of funding: \$0.2 million (fiscal years 2011 through 2012)

Description of project: This study explored the different breakdown of materials used in biodegradable stents and examined the potential effect of sex on the degradation of these materials.²

²Stents are mesh tubes used to improve circulation in narrow or weak arteries.

Select achievements reported by FDA: FDA reported that the study found that stent material breakdown varied in different tissues. The findings provide information that can guide FDA and the larger community in the design, manufacture, and evaluation of absorbable stents. FDA reported that this research will support the development of guidance for implants containing certain absorbable components.

Appendix II: Comments from the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation
Washington, DC 20201

APR 12 2016

Marcia Crosse
Director, Health Care
U.S. Government Accountability Office
441 G Street NW
Washington, DC 20548

Dear Ms. Crosse:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, "*Medical Product Oversight: FDA Needs More Strategic Planning to Guide its Scientific Initiatives*" (GAO-16-432).

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

A handwritten signature in cursive script that reads "Jim R. Esquea".

Jim R. Esquea
Assistant Secretary for Legislation

Attachment

**GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS)
ON THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED:
MEDICAL PRODUCT OVERSIGHT: FDA NEEDS MORE STRATEGIC PLANNING TO GUIDE
ITS SCIENTIFIC INITIATIVES (GAO-16-432)**

The U.S. Department of Health and Human Services (HHS) appreciates the opportunity to comment on GAO's findings in this draft report.

HHS recognizes the value of advancing regulatory science at FDA and concurs with the GAO's recommendations to improve strategic planning of regulatory science efforts. Advancing regulatory science across the breadth of FDA programs requires multiple, focused efforts that incorporate a variety of scientific expertise, effort, and insight from both FDA's internal and external stakeholders. FDA's Centers are responsible for the regulatory oversight of different product lines and are governed by different legal statutes and regulations, which have differing scientific standards and requirements that drive the particular needs related to advancing regulatory science. For example, the science needed to develop the methodologies to provide a meaningful pre-clinical assessment of potential toxicity for drugs, medical devices, and biologics require different considerations that necessitate different approaches. In addition, depending on the clinical indication, further considerations may be folded into the risk assessment performed regarding what level of evidence is required to start first-in-human clinical trials (i.e., vaccines going into healthy population vs. drug for life-threatening clinical indication).

FDA has a variety of stakeholders who promote scientific priorities and goals to advance specific interests. Congress establishes priorities, goals, and targets in legislation such as the Food and Drug Administration Amendments Act, the Food and Drug Administration Safety and Innovation Act, the Food Safety Modernization Act, the Drug Quality and Security Act, and the Sunscreen Innovation Act, etc., as well as through language in appropriations bills. The medical product centers operate under four distinct user fee programs, each with individually negotiated goals. While FDA does work to identify important priority areas for advancing regulatory science, the agency feels that specific scientific goals and deliverables are more appropriately set at the programmatic and project level, closer to the scientist reviewers who are in the best position to identify and respond to emerging regulatory science priorities.

To improve strategic planning for regulatory science efforts, GAO recommends that FDA take two actions. FDA should (1) develop and document measurable goals, including targets and timeframes, and (2) systematically track funding across its regulatory science priority areas.

GAO Recommendation #1: FDA should develop and document measurable goals, including targets and timeframes.

HHS Response: FDA agrees that efforts to advance regulatory science should be guided by broad strategic scientific priorities, but suggests that inclusion of detailed metrics for specific targets and timelines may be less appropriate for an agency level strategic plan. FDA proposes that documents with a more targeted focus, such as user fee commitment letters, specific

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programmatic planning documents and specific project proposals, are a more appropriate place to develop measurable goals with targets and timeframes.¹ This view is based on a number of considerations.

FDA must retain the flexibility to accommodate rapid shifts in its regulatory science priorities. It is important to note that a portion of regulatory science efforts at FDA are reactive, driven by rapidly emerging public health issues related to regulated products, advances in science and technology, or shifts in the medical product development and global markets. Thus, FDA must balance the utility of efforts and resources needed to develop a comprehensive long term strategic plan with detailed goals and targets against the need for maintaining flexibility and preparedness.

Setting broad priorities can provide guidance for the development of investigator initiated programs and projects that bring creative approaches to advancing scientific knowledge. Certain types of scientific efforts, such as developing the infrastructure and information base to support regulatory science, can be planned and executed in a predictable manner where targets and timelines are highly appropriate. Advancing scientific knowledge in a given area has an inherently uncertain and non-linear trajectory that makes setting specific targets and timelines challenging. Much of this trajectory is determined by the process of peer review where individual proposals are carefully examined for feasibility and merit, and subsequent successive outcomes build knowledge in an iterative way. By analogy, the National Institutes of Health clearly articulates goals for infrastructure, funding and generation of data (e.g. sequencing the human genome), but does not typically set targets for advancing scientific knowledge (e.g. planning how many disease cures should result from determining the human genome).

The regulatory science efforts that FDA has engaged in have, as noted in the GAO report, had a broad impact on internal and external stakeholders. FDA continues to be a good steward of its research programs, making effective use of its resources dedicated to advancing regulatory science. FDA regulatory science programs are highly productive and consistently advance regulatory science in ways that directly impact the effectiveness and efficiency of our regulatory review, creating new pathways for medical product development, enhancing our ability to provide useful guidance and advice to sponsors, and creating new technologies to monitor the manufacturing and real world use of approved medical products.

¹ In its report, the GAO noted a lack of specific goals, targets and timeframes in several FDA documents, including the 2011 and 2013 strategic documents. While these documents reflect broad areas of agency focus and communicate these effectively with external stakeholders, they were not intended as blueprints for the detailed management of FDA's regulatory science efforts. These strategic plans complement, but do not replace more specific planning documents.

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There are circumstances where there is a need to leave goal setting at a Center or program level due to specific needs; FDA is examining opportunities for setting agency level goals and targets where there are cross-cutting regulatory science needs that apply across the medical product centers. Examples may include planning for critical agency infrastructure to support regulatory science, the establishment of common programs related to scientific training and professional development, or the coordination of cross-cutting scientific efforts that are disease, rather than product centered. For these types of truly cross-cutting regulatory science efforts, FDA will work during its next strategic planning cycle to incorporate regulatory science priorities and goals into an integrated FDA strategic planning effort.

GAO Recommendation # 2: FDA should systematically track funding across its regulatory science priority areas

HHS: Response: FDA concurs with this recommendation. FDA Centers and Offices are currently looking at several models for how to improve the linkage and tracking of funding for regulatory science projects within the FDA nine priority areas. In doing so, the agency will be able to ascertain how spending is aligned with priority areas in a more systematic way.

For example, the Center for Drug Evaluation and Research (CDER) currently tracks at the project level all of its extramural funding and that portion of its intramural funding targeted to competitive intramural funding programs. This approach will be applied more systematically to include intramural projects funded through the CDER budget process, which will include new zero-based budgeting approach requiring that all budgetary line items be linked to specific priorities. In FY2016, the Center for Biologics Evaluation and Research (CBER) implemented a new system that provides for a more efficient use of tracking of resources at the project level to provide more accurate accounting for both resource allocation and expenditures. Additionally, CBER is linking research projects to FDA, Center, and Office-level priorities, goals, and objectives. CBER has also developed a new governance structure, the Regulatory Science Council, which will annually review its portfolio to determine that the research projects are aligned with the FDA, Center, and Office priorities, goals, and objectives, in order to make recommendations about resource allocations. The Center for Devices and Radiological Health (CDRH) is developing a Regulatory Science database to systematically track all regulatory science research projects including deliverables, metrics, and budget. CDRH is also using its Regulatory Science Subcommittee of the Center Science Council to develop regulatory science priorities, review projects for funding, and assess research programs to ensure the research aligns and impacts FDA and CDRH priorities. The National Center for Toxicological Research will continue to track all costs per project and, as of FY2016, is linking these to priorities specified in the FDA strategic plan.

Appendix III: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse, (202) 512-7114 or crossem@gao.gov.

Staff Acknowledgments

In addition to the contact name above, William Hadley, Assistant Director; Carolyn Garvey; Sandra George; Cathleen Hamann; Carolyn Feis Korman; and Deborah Linares made key contributions to this report.

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