FDA and Postapproval Drug Safety

A report released on April 21 by the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) on the performance of the agency's postmarket drug safety program indicated "substantial improvement" in oversight of drugs once they reach the public. The report, "Advances in FDA's Safety Program for Marketed Drugs," describes new scientific tools and capabilities that give the same priority to postmarket drug safety monitoring as to premarket drug review. The report also states that CDER is delivering earlier, more effective drug safety information to the public. In 2011, CDER issued 68 drug safety communications, up from 39 in 2010. The communications provide early information to patients and health care professionals about drug safety issues as they emerge.

CDER introduced a comprehensive plan to strengthen drug safety in 2004 that was enhanced with the passage of the FDA Amendments Act of 2007. The Act gave the FDA authority to require postmarket studies of drug safety concerns and drug labeling changes when new drug safety information is identified. Since 2008, the FDA has: required 65 safety-related labeling changes, in addition to the safety labeling changes effected voluntarily by drug manufacturers; required manufacturers to implement a variety of risk evaluation and mitigation strategies (REMS), including 64 complex REMS, to ensure that the benefits of a drug or biological product outweigh its risks; doubled staff members in CDER's Office of Surveillance and Epidemiology; and established specific safety positions within each of the Office of New Drugs' 18 divisions that review applications for new drugs.

Specific examples of the FDA's use of new drug safety tools include: the Mini-Sentinel pilot project, which enables FDA to assess medical product safety issues by utilizing secure access to the electronic health care information of more than 125 million patients, provided by 17 data partners nationwide; a new division in CDER's Office of Biostatistics that focuses exclusively on postmarket drug safety; an expanded program that enables FDA epidemiologists and statisticians to work with outside collaborators who have access to both large population-based health care data and the expertise to use those data for drug safety studies; and advances in pharmacogenomics to help doctors use genetic testing to anticipate the safety and effectiveness of a given drug for specific patients. More information is available at: www.fda.gov/Drugs/DrugSafety/ucm297389.htm.

U.S. Food and Drug Administration

CMS and Inpatient Quality of Care

The Centers for Medicare & Medicaid Services (CMS) on April 24 issued a proposed rule that would update Medicare payment policies and rates for inpatient stays to general acute care hospitals paid under the Inpatient Prospective Payment System (IPPS) and long-term care hospitals (LTCHs) paid under the LTCH Prospective Payment System (PPS). "The proposed rule would implement key elements of the Affordable Care Act's value-based purchasing program as well as the hospital readmissions reduction program. It also establishes the groundwork for extending Medicare's quality reporting programs beyond general acute care hospitals to other types of facilities," said CMS Acting Administrator Marilyn Tavenner. The proposed rule appeared in the May 12 issue of the *Federal Register*.

CMS is projecting that payment rates to general acute care hospitals will increase by 2.3% in FY 2013, a net update after inflation, improvements in productivity, a statutory adjustment factor, and adjustments for hospital documentation and coding changes. CMS projects that the rate increase, together with other policies in the proposed rule and projected utilization of inpatient services, would increase Medicare's operating payments to acute care hospitals by approximately 0.9% in FY 2013. After taking into account the expiration of certain statutory provisions that provided special temporary increases in payments to hospitals and other proposed changes to IPPS payment policies, CMS projects that total Medicare spending on inpatient hospital services will increase by about $175 million in FY 2013. CMS projects that LTCH payments will increase by approximately $100 million or 1.9% in FY 2013 under the proposed rule. CMS is proposing an annual update to LTCH payment rates of 2.1%, with certain specific deductions and adjustments.

The proposed rule would also strengthen the inpatient quality reporting program, with measures on perinatal care and readmissions, readmissions relating to hip and knee replacement procedures, and the use of surgery safety checklists. To provide hospitals with an incentive to reduce readmissions and improve care coordination, the Affordable Care Act required CMS to implement a Hospital Readmissions Reduction Program that will reduce payments beginning in FY 2013 (that is, for discharges on or after October 1, 2012) to certain hospitals that have excess readmissions for: cardiac events, heart failure, and pneumonia.

CMS will accept comments on the proposed rule until June 25 and will respond to all comments in a final rule to be issued by August 1.

Centers for Medicare & Medicaid Services

FDA PMA Guidance

The U.S. Food and Drug Administration (FDA) on March 27 pub-

lished a first-of-a-kind guidance for medical device manufacturers, describing the process by which benefits and risks of certain medical devices are considered during premarket review. Premarket approval (PMA) is the FDA review process used to evaluate the safety and effectiveness of Class III medical devices. Class III devices are those that support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury. The de novo process is available for low- and moderate-risk devices that have been found not substantially equivalent (NSE) to existing devices. When evaluating PMA applications or de novo petitions, the FDA relies on valid scientific evidence to assess safety and effectiveness. Both clinical and nonclinical data play a role in FDA's benefit/risk determinations.

The new guidance includes a worksheet for device reviewers that incorporates factors that influence benefit/risk determinations, such as the type, magnitude, and duration of a risk or benefit, the probability that a patient will experience the risk, patient tolerance for risk, availability of alternative treatments, and the value the patient places on treatment. The guidance: (1) outlines the systematic approach FDA device reviewers take when making benefit/risk determinations during the premarket review process; (2) provides manufacturers a tool that explains the various factors considered by the agency during the review of PMA applications, the regulatory pathway for high-risk medical devices, and de novo petitions; and (3) describes an approach that takes into account patients' tolerance for risks and perspectives on benefits, as well as the novelty of the device.

"This guidance clarifies this process for industry, which will provide manufacturers with greater predictability, consistency, and transparency in FDA decision making while allowing manufacturers and the FDA to use a common framework for benefit-risk determinations," said Jeffrey Shuren, MD, director of the FDA Center for Devices and Radiological Health (CDRH). CDRH will train medical officers, review staff managers, and device reviewers on the guidance to assure that it is applied consistently to submissions and petitions. CDRH reviewers began applying the guidance to incoming PMA and de novo submissions and to submissions already under review with decisions starting on May 1. The FDA is also developing external training modules to help industry and device sponsors understand how CRDH will apply the guidance. More information is available at: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/default.htm.

U.S. Food and Drug Administration

DOE and Massive Datasets

On March 29, U.S. Department of Energy (DOE) Secretary Steven Chu, PhD, announced the award of $5 million to establish the Scalable Data Management, Analysis, and Visualization (SDAV) Institute as part of the Obama Administration's "Big Data Research and Development Initiative," which was announced on the same day and takes aim at improving the nation's ability to extract knowledge and insights from large and complex collections of digital data. Led by the DOE Lawrence Berkeley National Laboratory, the SDAV Institute will bring together the expertise of 6 national laboratories and 7 universities to develop new tools to help scientists manage and visualize data on DOE supercomputers.

The SDAV Institute will help scientists better extract insights from increasingly massive research datasets by assisting researchers in using state-of-the art software tools for data analysis on these supercomputers. These tools will range from superfast search engines to sophisticated visualization software that enables researchers to literally picture and "see" complex relations among data points. DOE supports some of the world's fastest supercomputers, which are used by scientists from a wide range of fields.

In addition to the Berkeley Lab, the SDAV team includes experts from Argonne, Lawrence Livermore, Los Alamos, Oak Ridge, and Sandia National Laboratories, as well as from the Georgia Institute of Technology, North Carolina State University, Northwestern University, The Ohio State University, Rutgers University, University of California at Davis, and University of Utah. Kitware, a company that develops and supports specialized visualization software, is also a partner in the project and will accelerate deployment of the technologies that the institute develops into the private sector. Subject to congressional appropriations, the department plans to make an additional $20 million available over the next 4 y to fully fund the institute. For more information on the SDAV Institute, visit http://sdav-scidac.org/.

U.S. Department of Energy

Cloud Access to Genome Data

The National Institutes of Health (NIH) announced on March 29, as part of the White House Office of Science and Technology Big Data Initiative, that the world's largest set of data on human genetic variation—produced by the international 1000 Genomes Project—is now publicly available on the Amazon Web Services (AWS) cloud. The Big Data initiative will initially engage at least 6 federal science agencies, committing more than $200 million to a collaborative effort to develop core technologies and other resources needed by researchers to manage and analyze extremely large datasets.

Among the NIH components participating in the Big Data initiative are the National Human Genome Research Institute (NHGRI) and the NIH National Center for Biotechnology Information (NCBI), a division of the National Library of Medicine. NHGRI played a lead role in organiz-

ing and funding the international 1000 Genomes Project. NCBI, along with the European Bioinformatics Institute (Hinxton, England), began making 1000 Genomes Project data freely available to researchers in 2008. Since the project's launch, the dataset has grown rapidly: at 200 terabytes—the equivalent of 16 million file cabinets filled with text, or more than 30,000 standard DVDs—the current 1000 Genomes Project records are an example of big data that have become so massive that few researchers have the computing power to use them easily or effectively.

To resolve this challenge, AWS has posted the 1000 Genomes Project data for free as a public dataset, providing a centralized repository on the Amazon Simple Storage Service. Data can be accessed through services such as Amazon Elastic Compute Cloud and Amazon Elastic MapReduce, which provide organizations with the highly scalable resources needed to power big data and high-performance computing applications. Researchers pay only for additional AWS resources needed to further process or analyze the data. The public/private collaboration to store the data in the AWS cloud allows researchers to access and analyze data at a fraction of the cost it would take for their institutions to acquire the needed Internet bandwidth, data storage, and analytical computing capacity. Cloud access also enables users to analyze data much more quickly, eliminating time-consuming downloads and allowing users to run analyses over many servers at once.

Initiated in 2008, the 1000 Genomes Project aims to build the most detailed map of human genetic variation, ultimately with data from the genomes of more than 2,600 people from 26 populations around the world. The project began with 3 pilot studies that assessed strategies for producing a catalog of genetic variants that are present at $\geq$1% in the populations studied. Data from the pilot studies were released on AWS in 2010. Data now being released in the cloud include results from sequencing the DNA of some 1,700 people; the remaining 900 samples will be sequenced in 2012, and those data will be released to researchers as soon as possible. The new results identify genetic variation occurring in $<$1% of the study populations.

The 1000 Genomes Project welcomes working with other cloud computing providers who are interested in hosting the data. Cloud access to the 1000 Genomes Project data through AWS is at http://s3.amazonaws.com/1000genomes/. The 1000 Genomes Project data are also freely available through the 1000 Genomes website, at www.1000genomes.org.

As part of the Big Data initiative, NIH will join with the National Science Foundation to fund the development of core technologies for data collection, management, analysis, and extraction. NIH is particularly interested in imaging, molecular, cellular, electrophysiological, chemical, behavioral, epidemiological, clinical, and other data sets related to health and disease.

National Institutes of Health

Global Safety Initiative

The U.S. Food and Drug Administration (FDA) on April 23 released the agency's "Global Engagement Report," detailing the activities and strategies the agency is using to transform from a domestic to a global public health agency. The report describes the steps the agency is taking to ensure that imported food, drugs, medical devices, and other regulated products meet the same rigorous standards for safety and quality as those manufactured within the United States. Global production of FDA-regulated goods and materials has expanded rapidly over the last decade and continues to grow. FDA-regulated products originate from more than 150 countries, 130,000 importers, and 300,000 foreign facilities. Each year from 2005 to 2011, food imports have grown by an average of 10%, imports of pharmaceutical products have increased at nearly 13%, and device imports have grown more than 10%. More than 80% of active pharmaceutical ingredients used to make medicines are imported.

The report outlines a variety of engagement strategies the FDA is using in partnership with other agencies, organizations, and coalitions around the world to strengthen global, regulatory capacity-building efforts; develop and harmonize science-based regulatory standards; increase awareness about the importance of regulatory systems; and share information and data globally to facilitate rapid identification of and response to public health emergencies. Through its international offices in Africa, Asia, Europe, Latin America, and the Middle East, the FDA is increasing global understanding of FDA regulations and standards for products destined for U.S. consumers and collaborating to strengthen regulatory science and evidence-based approaches to product safety and quality. The report and more information are available at: www.fda.gov/global.

U.S. Food and Drug Administration