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The FDA as a Public Health Agency

Margaret A. Hamburg, M.D., and Joshua M. Sharfstein, M.D.

A little more than a century ago, concerned about the potential dangers of food preservatives such as formaldehyde, Congress passed, and President Theodore Roosevelt signed, the Pure Food and Drug Act. The act sought to prevent the "manufacture, sale, or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs, medicines, and liquors." The office initially charged with this responsibility was the Bureau of Chemistry of the Department of Agriculture.

Since that time, the bureau has grown into the Food and Drug Administration (FDA), an agency in the Department of Health and Human Services (DHHS) responsible for oversight of more than $2 trillion in medical products, food, and other consumer goods. What has remained constant is the agency's "overriding purpose," in the words of the Supreme Court, of protecting the public health.[1] As the new commissioner and principal deputy commissioner of the FDA chosen by President Barack Obama, we would like to provide a broad overview of how we intend to embrace this role.

The Institute of Medicine has defined the mission of public health as "fulfilling society's interest in assuring the conditions in which people can be healthy." To be healthy, people need access to a safe and nutritious food supply and to innovative, safe, and effective medical products. The FDA's job is to support this access and, in doing so, to promote health, prevent illness, and prolong life. The ultimate measures of the FDA's success should reflect its fundamental goals and go beyond such intermediate measures as the number of facilities inspected or drugs approved.

The urgent need to develop and produce a vaccine against H1N1 influenza virus provides an illustration of the agency's public health role. Laboratory scientists at the FDA are growing the virus and will make reagents for vaccine-potency testing, reviewers will help to design and oversee the clinical trials, and inspectors will oversee the quality of the production process. The agency's success will be determined by the nation's access to a safe and effective vaccine.

The traditional tools of a regulatory agency are regulation, approval or disapproval of applications, and enforcement. As a public health agency, the FDA should always ask whether delays in approval or safety problems can be prevented — a mandate that requires extensive and creative engagement with regulated industries, patient and consumer groups, and others. The FDA should actively pursue opportunities to help advance science in the domains it regulates and ad-

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The New Sentinel Network — Improving the Evidence of Medical-Product Safety

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In 2007, Congress directed the Food and Drug Administration (FDA) to create a new postmarketing surveillance system that will, by 2012, be using electronic health data from 100 million people to prospectively monitor the safety of marketed medical products.[1] This new system is intended to complement existing systems of "spontaneous" adverse-event reporting. In May 2008, the FDA announced the Sentinel Initiative, which would "access the capabilities of multiple, existing data systems (i.e., electronic health record systems, medical claims databases)."[2] The network of data systems is intended both to detect signals (i.e., higher-than-expected rates of adverse outcomes) and to confirm signals, including those suggested by other sources, and to do so rapidly and quantitatively. At a recent Senate hearing before her confirmation, FDA Commissioner Margaret Hamburg stated that close postmarketing monitoring of medical-product safety would remain a high priority during her tenure.[3]

Achieving these goals requires the first large-scale, truly integrated use of the electronic data that are increasingly available in our pluralistic health care system. The first hurdles are determining how best to organize the Sentinel Network, how it should operate, and what steps are needed for its implementation.

Initially, the Sentinel Network will rely on electronic medical records and administrative data that are routinely collected by medical practices, hospitals, delivery systems, health plans, and insurers. Medicare and Medicaid databases of prescriptions and other information on the use of medical resources could be an important large-scale data source. Eventually, the network might also use information from disease registries and vital-statistics registries, as well as repositories of genomics data.

The goals of the Sentinel Initiative can be achieved without the creation of a large centralized database. In a distributed data network, participating organizations would maintain control of their data, create data files in a standard format, summarize data by running computer programs distributed by a coordinating center, and then provide consistent summarized results that could be combined to provide networkwide results. For example, the programs could identify persons within each organization who had been exposed to specific drugs, compute

The Rosiglitazone Story — Lessons from an FDA Advisory Committee Meeting

Clifford J. Rosen, M.D.

On July 30, 2007, the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee of the Food with long-term nitrate use and those receiving concomitant insulin therapy. Still, there were several caveats inherent in the meta-analyses, including the facts that government agency subjected to pressure from industry, had caused undue harm to patients. Notwithstanding this characterization, as well as the emotional nature of

July 30, 2007:
Endocrinologic and Metabolic Drugs Advisory Committee Meeting

Revisiting the Rosiglitazone Story — Lessons Learned

Clifford J. Rosen, M.D.

In July 2007, 24 members of the Endocrinologic and Metabolic Drug Advisory Committee (EMDAC) and the Drug Safety and Risk Management Advisory of the joint advisory committee met for 20 hours over 2 days to further advise the FDA about rosiglitazone. Ultimately, the committee agreed that the drug posed formin, the hazard ratio is lower, although it is still greater than 1. In comparison with the FDA's 2007 meta-analysis, the newer analyses showed higher odds ra-

July 13-14, 2010:
Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

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OCTOBER 14, 2010

Regulatory Action on Rosiglitazone by the U.S. Food and Drug Administration

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There have been ongoing concerns about the safety of the diabetes drugs containing rosiglitazone (Avandia, Avandaryl, and Avandamet) — a thiazolidinedione antidiabetic agent indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

In 2007, a meta-analysis of controlled clinical trials found increases in the risk of myocardial infarction and a near-significant increased risk of death from cardiovascular causes when rosiglitazone was compared with placebo or with standard diabetes drugs.[1] Following an advisory committee meeting held in July 2007, the U.S. Food and Drug Administration (FDA) added information about the possibility of ischemic cardiovascular risk to the drug's existing boxed warning. At the same time, the FDA also required the sponsors to conduct a head-to-head cardiovascular safety trial of rosiglitazone versus pioglitazone — the other antidiabetic drug in this class available in the United States. After new data became available, the FDA held a second advisory committee meeting on rosiglitazone safety on July 13 and 14, 2010. On September 23, 2010, the FDA announced regulatory actions stemming from these deliberations.

The FDA is restricting access to rosiglitazone by requiring the drug sponsor to submit a Risk Evaluation and Mitigation Strategy, or REMS. Under the Food and Drug Administration Amendments Act of 2007, the FDA can require a drug sponsor to issue a REMS to impose certain restrictions so that the benefits of a drug continue to outweigh its risks. When the REMS for rosiglitazone is implemented, the drug will be available to patients not already taking it only if they are unable to achieve glycemic control using other medications and, in consultation with their health care professional, decide not to take pioglitazone for medical reasons. Current users of rosiglitazone will be able to continue using the medication if they appear to be benefiting from it and they acknowledge that they understand these risks. Doctors will have to attest to and document their patients' eligibility; patients will have to review statements describing the cardiovascular safety concerns.

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Effect of Sibutramine on Cardiovascular Outcomes in Overweight and Obese Subjects

W. Philip T. James, M.D., D.Sc., Ian D. Caterson, M.D., Ph.D., Walmir Coutinho, M.D., D.Sc., Nick Finer, M.B., B.S., Luc F. Van Gaal, M.D., Ph.D., Aldo P. Maggioni, M.D., Christian Torp-Pedersen, M.D., Ph.D., Arya M. Sharma, M.D., Ph.D., Gillian M. Shepherd, B.Sc., Richard A. Rode, Ph.D., and Cheryl L. Renz, M.D., for the SCOUT Investigators*

EDITORIALS

Sibutramine — Another Flawed Diet Pill

Gregory D. Curfman, M.D., Stephen Morrissey, Ph.D., and Jeffrey M. Drazen, M.D.

September 15-16, 2010:
Endocrinologic and Metabolic Drugs Advisory Committee Meeting

FDA Officials Discuss FDA Actions

Erythropoiesis-Stimulating Agents — Time for a Reevaluation

Ellis F. Unger, M.D., Aliza M. Thompson, M.D., Melanie J. Blank, M.D., and Robert Temple, M.D.

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The FDA and Safe Use of Long-Acting Beta-Agonists in the Treatment of Asthma

Badrul A. Chowdhury, M.D., Ph.D., and Gerald Dal Pan, M.D., M.H.S.

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Weighing Risks and Benefits of Liraglutide — The FDA's Review of a New Antidiabetic Therapy

Mary Parks, M.D., and Curtis Rosebraugh, M.D., M.P.H.

N ENGL J MED 362;9 NEJM.ORG MARCH 4, 2010

The Safety of Tiotropium — The FDA's Conclusions

Theresa M. Michele, M.D., Simone Pinheiro, Sc.D., and Solomon Iyasu, M.D., M.P.H.

N ENGL J MED 363;12 NEJM.ORG SEPTEMBER 16, 2010

Weighing Benefits and Risks — The FDA's Review of Prasugrel

Ellis F. Unger, M.D.

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NEJM Publication of Sentinel Findings

Ad Hoc Sentinel Queries

- **Online Only on FDA section of *NEJM* Health Policy Website**
- **Peer review: focused review, narrowly tailored to Sentinel information**

Planned Sentinel Evaluations

- **Perspective articles or Special Reports**
- **Peer review: rapid review, 48-hour turnaround**


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