

REVIEW ARTICLE

Edward W. Campion, M.D., *Editor*

FDA Regulation of Prescription Drugs

Audrey L. Gassman, M.D., Christine P. Nguyen, M.D.,
and Hylton V. Joffe, M.D., M.M.Sc.

From the Division of Bone, Reproductive, and Urologic Products, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD. Address reprint requests to Dr. Joffe at the Division of Bone, Reproductive, and Urologic Products, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002, or at hylton.joffe@fda.hhs.gov.

This article was updated on March 13, 2017, at NEJM.org.

N Engl J Med 2017;376:674-82.

DOI: 10.1056/NEJMra1602972

Copyright © 2017 Massachusetts Medical Society.

IN 2015, APPROXIMATELY 4 BILLION PRESCRIPTIONS WERE FILLED AT RETAIL pharmacies in the United States.¹ The Center for Drug Evaluation and Research (CDER) within the Food and Drug Administration (FDA) ensures that prescription drugs have reliable quality and purity and that they provide benefits that outweigh the risks for the intended population.² The FDA does not develop drugs or conduct clinical trials; drug companies are responsible for those activities, with important contributions from universities and academic medical centers.³ The FDA provides guidance to drug companies, evaluates the data generated from their programs, and then determines whether a drug can be approved. The criteria for approval are substantial evidence of effectiveness and benefits that outweigh the risks and remaining uncertainties.⁴ After approval, the FDA monitors drugs by means of various data sources, including clinical trials, epidemiologic studies, and postmarketing reports.⁵ The purpose of this article is to provide clinicians who prescribe FDA-approved drugs with an understanding of the key aspects of drug regulation. We focus on CDER activities and data and do not cover products regulated by other FDA centers.

FDA DRUG-REVIEW PROCESS

Drug companies are required to establish the effectiveness and safety of new drugs before marketing them.⁶ For substantial evidence of effectiveness, regulations require reports from “adequate and well-controlled investigations.”⁷ The plural form of “investigation” is interpreted as meaning that evidence from at least two adequate and well-controlled trials is required to support effectiveness. Positive results from two trials, as compared with a single trial, provide greater assurance that the findings are not due to chance or bias. However, the FDA can accept evidence from a single trial — for example, if a second trial is not feasible (e.g., in the case of a rare disease) or would be unethical (e.g., when a convincing survival benefit is shown in one trial) or if there is supporting evidence from related uses (e.g., evidence from another trial that tested the drug in a different phase of the disease in question).⁸⁻¹⁰ One study¹¹ reported that approximately one third of new-drug approvals between 2005 and 2012 were based on a single pivotal trial. We found that for the 2011–2015 period, about 50% of new-drug approvals were based on a single pivotal trial, and nearly two thirds of those approvals were for the treatment of rare diseases (Drugs@FDA database).¹² The law does not require a new drug to be better than, or as good as, another approved drug, but the FDA takes into account available treatments when determining whether a drug’s benefits outweigh its risks.

STRUCTURED FRAMEWORK FOR BENEFIT–RISK ASSESSMENT

The FDA has recently started implementing a new structured framework for assessing benefits and risks. The framework covers the target condition and available

treatments, the benefits and risks of the drug under review, and strategies for managing risks.¹³

Analysis of the Target Condition and Available Treatments

An analysis of the target condition and available treatments provides the context for weighing a drug's benefits and risks. For example, a drug intended to treat patients with a life-threatening disease for which no therapy is currently available may have benefits that outweigh its risks even if those risks would be considered unacceptable for a condition that is not life-threatening.

Assessment of Benefits and Risks

The benefit–risk assessment is based on information submitted in the marketing application, with uncertainties arising from imperfect data (e.g., conflicting findings, missing data, and other limitations) taken into account. For example, trials cannot feasibly assess rare side effects (sample sizes would be prohibitively large) or long-term (e.g., decades-long) administration of drugs. In addition, the study population is typically narrower than the patient population that will use the drug, if approved.¹⁴ Other considerations include the magnitude and durability of the benefit and its effect on how patients feel and function, the adequacy of the safety data, the severity and reversibility of side effects, and the anticipated real-world use of the drug.

Strategies for Managing Risks

All drugs have risks. The primary tool for managing risk is the FDA-approved drug label. If risk minimization strategies in addition to the label are needed to ensure that the drug's benefits outweigh its risks, the FDA will require a Risk Evaluation and Mitigation Strategy (REMS). The label and REMS are described below.

THE DRUG-REVIEW TEAM

A drug-review team at the FDA includes project managers, chemists, nonclinical pharmacologists and toxicologists, clinical pharmacologists, statisticians, physicians, experts in drug labeling and in medication-error prevention and risk management, and inspectors of clinical trial and manufacturing sites. If there are complicated efficacy or safety issues, an advisory committee is convened to obtain advice from outside experts, who are rigorously screened for conflicts of in-

terest, and to hear from the public.¹⁵ According to a 2012 report,¹⁶ an advisory committee was involved in the review process for 37% of new drugs approved during the 2001–2010 period. We found similar results for the 2011–2015 period (Drugs@FDA database).¹² The FDA considers the recommendations of the advisory committee but is not required to follow them.

APPROVAL OF DRUGS

The FDA will approve a drug if there is substantial evidence of effectiveness for the proposed use and if the benefits outweigh the risks and remaining uncertainties. The drug's quality and manufacturing processes must also meet rigorous standards before approval.¹⁷ After approval, the FDA publishes on the Drugs@FDA website its comprehensive scientific reviews, the decisional memorandum explaining the reasoning for approving the drug, and the approved drug label.¹²

BRAND-NAME DRUGS

The FDA approved 204 new drugs in the 2011–2016 period; about 40% of these approvals were for first-in-class drugs, and about 40% were for the treatment of rare diseases (Fig. 1).¹⁸ A drug company extensively tests a new drug in the laboratory, in animals, and in humans and has multiple interactions with the FDA before submitting a marketing application.⁴ This application, which may contain thousands of pages, includes drug chemistry, quality, and manufacturing data; safety information from in vitro and animal studies; clinical pharmacologic data (e.g., drug-interaction studies); and clinical trial data. The time from submission of the application to the FDA's decision is usually 6 to 12 months, with the shorter time reserved for certain situations, such as a drug that is intended for the treatment of a serious condition and that appears to provide an important advance in safety or effectiveness.¹⁹ Not all marketing applications can be approved, and some are approved only after the company has provided additional data that are reviewed in one or more subsequent review cycles. For example, the FDA approved 50% of first-time marketing applications for new drugs that were submitted between 2000 and 2012. Approximately 50% of the unsuccessful applications were approved by mid-2013, after the issues raised had been resolved.²⁰ Problems identified in the unapproved

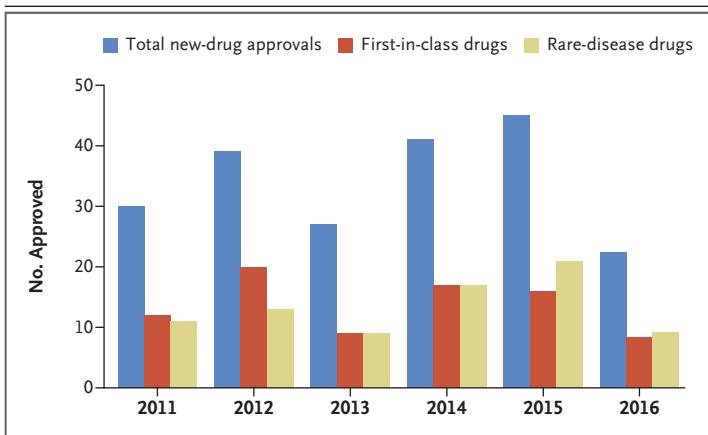


Figure 1. New Drugs Approved by the Food and Drug Administration, 2011–2016.

Data are from the Center for Drug Evaluation and Research within the Food and Drug Administration.¹⁸ New drugs are molecular entities that have never been approved before, as well as new therapeutic biologic products. Total new-drug approvals include first-in-class drugs and drugs that are not first-in-class (i.e., drugs that are new molecular entities but have actions similar to those of earlier drugs and do not necessarily offer unique clinical advantages). Rare (“orphan”) diseases are defined as those that affect 200,000 or fewer persons in the United States. First-in-class drugs and rare-disease drugs are not mutually exclusive categories.

first-time applications included dose-selection issues (16%), poor efficacy (13%), inconsistent results across end points (13%) or across trials or study sites (11%), and safety deficiencies (53%).²⁰ Approvals of first-time marketing applications for new drugs reached nearly 80% of submitted applications in 2013 and nearly 90% in 2014 (www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM477020.pdf).

GENERIC DRUGS

Nearly 90% of prescriptions filled in the United States are for generic drugs.²¹ A generic drug must be equivalent to the brand-name drug in terms of dosage form, safety, strength, route of administration, quality, and intended use but in most cases does not need to have the same inactive ingredients.²² The generic drug must also be bioequivalent to the brand-name drug. A common approach to demonstrating bioequivalence is to show statistically that there is no significant difference in the rate and extent of absorption between the brand-name and generic drugs, on the basis of frequent measurements of blood, plasma, or serum concentrations.²³ Clinical stud-

ies may be needed for drugs that are not appreciably absorbed into the bloodstream.

THE FDA-APPROVED DRUG LABEL

The FDA-approved label contains a summary of information necessary for safe and effective use of the drug. The FDA and the drug company ensure that the final label contains pertinent and substantiated information. The information on the label must not be false, misleading, or promotional.²⁴

Any section of the label can be revised when necessary. Most revisions must be approved by the FDA before implementation. Before 2007, the FDA could request but not require (short of threatening to withdraw approval, if appropriate) that the drug company update the label with important new safety information. This sometimes led to protracted and difficult labeling discussions. The 2007 Food and Drug Administration Amendments Act gave the FDA the authority to require and, if necessary, order safety-related label changes on the basis of new safety information.²⁵ Since 2007, the FDA has occasionally ordered safety-related label changes,²⁶ but most labels are appropriately revised to address new safety information in a timely manner without the need for an order.

All brand-name drugs approved since June 2001 and certain drugs approved before June 2001 (e.g., those approved for new uses after June 2001) must have prescribing information in Physician Labeling Rule (PLR) format.²⁷ PLR format makes drug labels easier to access and read, facilitating prescribing decision making. The PLR-formatted label has three main sections: Highlights of Prescribing Information, Table of Contents, and Full Prescribing Information. The Highlights section, which is typically half a page, provides the critical information needed for safe and effective use of the drug and includes hyperlinks to more detailed information in the Full Prescribing Information section of the label. The Full Prescribing Information section is divided into numbered sections and subsections ordered according to clinical relevance (Table 1).

MITIGATING RISKS

Certain drugs have such serious risks that the FDA may require a REMS to mitigate the particular risks and ensure that the drug's benefits outweigh the risks.²⁸ The FDA considers the risks in

the context of the drug's benefits when deciding whether a REMS is required. For example, for the same risk, one drug approved for the treatment of a life-threatening condition may not need a REMS, but another drug approved for the treatment of a non-life-threatening condition may require a REMS. The FDA can require a REMS for a drug with or after approval of the marketing application, depending on when the serious risk is identified.

A REMS includes at least one of the following components: a Medication Guide, a communication plan for health care providers, and "elements to assure safe use" (ETASUs).²⁸ The components can be used together to achieve the goals of the REMS.

A Medication Guide, which is written for patients and caregivers, conveys important information about the risks associated with a drug and actions that the patient can take to prevent or mitigate a serious adverse reaction.²⁹ For example, topical testosterone gels and solutions have a Medication Guide that provides information about the risk of testosterone transfer to women and children when they have skin-to-skin contact with the application site of a treated man.³⁰ The Medication Guide describes steps to reduce this risk, such as washing and covering the application site with clothing. A drug can also have a Medication Guide that is not part of a REMS. When a drug has a Medication Guide, federal law requires that the guide be given to the patient each time the drug is dispensed outside the hospital setting.³¹

A communication plan typically consists of FDA-approved letters and other printed materials that the drug company is required to disseminate, alerting health care providers about serious risks. For example, insulin inhalation powder has a communication plan because it carries a risk of acute bronchospasm in patients with chronic lung disease.³⁰ This communication plan includes letters to health care providers and professional societies, a fact sheet distributed to likely prescribers, and a website consisting of REMS materials.

ETASUs are interventions or other actions that health care providers, pharmacies, patients, or other components of the health care system must take before the drug is prescribed, dispensed, or used (Table 2). For example, vigabatrin, an anticonvulsant agent, has a REMS with an ETASU to ensure that health care providers are educated

about the risk of permanent vision loss, the need to counsel patients about this risk, and the need for periodic ophthalmic monitoring.³⁰ The REMS also ensures that vigabatrin is dispensed to patients who have documentation showing that they have been informed about this risk and the need for periodic ophthalmic monitoring.

Drug companies are required to periodically assess their REMS programs (e.g., by surveying health care providers, patients, or both to determine their understanding of the risks addressed by the REMS). If, on review of these assessments, the FDA finds that goals of the REMS have not been adequately met, the FDA has the authority to require changes to the REMS. During these reviews, the FDA also considers whether the REMS is still necessary or whether a change in the REMS is needed to reduce the burden. As of December 2016, there are 75 approved REMS programs. Health care providers can search for REMS programs by drug name on the REMS@FDA website.³⁰

POSTMARKETING SURVEILLANCE

Even with extensive testing, it is not possible to know all the side effects of a drug before approval, particularly rare side effects or those that take a long time to develop. After approval of a drug, the FDA uses data from various sources to monitor and assess drug safety during real-world use,³² such as the FDA Adverse Event Reporting System (FAERS),³³ postmarketing epidemiologic studies or clinical trials, published reports, and the Sentinel System.³⁴

FDA ADVERSE EVENT REPORTING SYSTEM

FAERS is a database containing reports on adverse events, product quality, and medication errors that are submitted by health care providers, consumers, and drug companies. Since 1969, more than 12 million reports have been collected.³³ FAERS is useful for detecting rare events (e.g., fulminant liver failure in a population not predisposed to liver failure) and unusual events occurring shortly after drug exposure (e.g., anaphylaxis). For example, on the basis of adverse-event reports, the FDA identified a constellation of disabling and potentially irreversible adverse reactions involving the tendons, muscles, joints, and nervous system that was associated with the use of systemic fluoroquinolone antibiotics. However, FAERS has important limitations: reporting is

Table 1. Organization and Content of the Full Prescribing Information.*

Section	Type of Information Included
Boxed Warning (sometimes referred to in lay terms as a “black-box warning”)	Contraindications or warnings about serious adverse reactions† that may lead to death or serious injury; placed prominently at the beginning of the Full Prescribing Information and outlined by a single black line.
1. Indications and Usage	FDA-approved uses that are supported by substantial evidence of effectiveness, with benefits that outweigh the risks
2. Dosage and Administration	Recommended starting dosage, dose adjustments (titration), maximum dosage; route of administration; dosage modifications needed owing to drug interactions and food interactions or in specific populations (e.g., patients with renal or hepatic impairment or pediatric patients); and important instructions about administration (e.g., reconstitution and preparation instructions)
3. Dosage Forms and Strengths	Approved dosage forms and strengths
4. Contraindications	Situations in which the risk clearly outweighs any possible therapeutic benefit and the drug must not be used
5. Warnings and Precautions	Important risks associated with the drug and information about how to prevent, mitigate, or monitor the risk or adverse reaction
6. Adverse Reactions	Overall adverse-reaction profile of the drug from clinical trials, including common adverse reactions, and adverse reactions reported in the postmarketing arena
7. Drug Interactions	Clinical implications of relevant drug interactions, with instructions for preventing or managing the interactions (e.g., dose adjustment or avoiding use of the other drug)
8. Use in Specific Populations	Information about use of the drug during pregnancy and lactation, in persons with reproductive potential, in the pediatric and geriatric populations, and in patients with certain coexisting conditions (e.g., renal or hepatic impairment)
9. Drug Abuse and Dependence	Information on a drug’s potential for abuse, misuse, addiction, dependence, and tolerance and about a drug’s abuse-deterrent properties
10. Overdosage	Signs, symptoms, laboratory findings, and complications of overdose and how to treat an overdose
11. Description	Chemical characteristics of the drug (e.g., nomenclature, dosage forms, structural formula, and a list of active and inactive ingredients)
12. Clinical Pharmacology	Information on the mechanism of action, if known, and the drug’s pharmacokinetic and pharmacodynamic effects
13. Nonclinical Toxicology	Information on the propensity of the drug to cause cancer in animals, effects of the drug on the fertility of animals, and other toxicologic and pharmacologic findings in animals
14. Clinical Studies	Summary of the trial designs and results that established substantial evidence of effectiveness
15. References	Usually omitted, unless there are authoritative references that contain information that is not in the label and that is important for the health care provider
16. How Supplied and Storage and Handling	Dosage forms, strengths, quantity of product available for prescribing (e.g., bottles of 100 tablets or 60-g tubes) and storage and handling conditions (e.g., whether the product should remain at room temperature or be refrigerated)
17. Patient Counseling Information	Important information that the health care provider should convey to the patient or caregiver when a counseling decision is taking place (e.g., major risks of the drug and critical administration instructions)

* Sections of the label that are not pertinent to the specific drug are omitted from the label. See Code of Federal Regulations, 21 CFR 201.57(c) (<https://www.gpo.gov/fdsys/pkg/CFR-2016-title21-vol4/pdf/CFR-2016-title21-vol4-sec201-57.pdf>), for all the requirements for these sections, and see labeling guidance documents for FDA recommendations for many of these sections (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>).

† For the purposes of the label, an adverse reaction is an undesirable effect, reasonably associated with the use of a drug, for which there is some basis to believe that there is a causal relationship between the drug and the occurrence of the undesirable effect.

voluntary (so it cannot be used to calculate the incidence of an adverse event), causality can be difficult to determine, and reports may lack the details required to properly evaluate an event.³³ FAERS is also not useful for evaluating adverse

events that are common in the treated population, such as acute myocardial infarction in statin users.

Health care providers and consumers can submit reports to FAERS, through the postal service, by fax, or on the FDA’s MedWatch website,³⁵ or

Table 2. Elements to Assure Safe Use (ETASUs).*

Element	Example
Health care providers who prescribe the drug must have specified training or experience or be specially certified.	Prescribers must pass a knowledge-assessment test about the serious risk and actions to mitigate the risk.
Pharmacies, practitioners, or health care settings that dispense the drug must be specially certified.	Before dispensing the drug, the pharmacy must verify that the prescriber is certified under the REMS to prescribe the drug.
The drug must be dispensed only in certain settings.	The drug must be dispensed or administered only at infusion centers or hospitals, not at outpatient pharmacies.
The drug must be dispensed only if there is evidence or documentation of safe-use conditions, such as laboratory test results.	A negative pregnancy test is required for a drug that has a risk of teratogenicity before the drug is prescribed or refilled.
Each patient using the drug must be subject to specific monitoring.	Liver tests are required at specified intervals for a drug that has hepatotoxic effects.
Each patient using the drug must be enrolled in a registry.	Enrollment of all patients in a registry is required in order to obtain better information about the risk.

* When drugs are approved with an ETASU, at least one of these elements must be included in the Risk Evaluation and Mitigation Strategy (REMS).

to the drug company. The reports should include sufficient details so that the FDA can properly evaluate them (Table 3). When a detailed assessment suggests a safety concern, the FDA can take regulatory action, such as updating the drug label, publicly communicating the new safety information, requiring a REMS, or requiring studies to further evaluate the safety signal. For example, on the basis of FAERS reports of testosterone transfer to children,³⁶ the FDA requires a boxed warning and a REMS with a Medication Guide for topical testosterone gels and solutions that have been approved and also requires studies of testosterone transfer for new topical testosterone products.

EPIDEMIOLOGIC STUDIES

Epidemiologic studies that make use of administrative health care claims data, electronic medical records, or other prospective data beyond those collected for routine care can be useful for assessing or quantifying a risk associated with drug exposure, particularly when randomized trials are not feasible or are unethical or when drug effects are being assessed in a broader population than the populations enrolled in the clinical trials.³⁷ Although epidemiologic studies lack randomization and may have biases that limit interpretability, well-designed and well-conducted studies can yield interpretable data.^{37,38} For example, the FDA required that information about QT-interval prolongation and torsades de pointes

be added to azithromycin labels, a decision based, in part, on an epidemiologic study that showed a higher risk of death from cardiovascular causes with azithromycin than with amoxicillin, ciprofloxacin, or no drug treatment.^{39,40}

SENTINEL SYSTEM

The full Sentinel System, which was launched in February 2016, allows the FDA to securely use the existing electronic health care data of more than 190 million patients, provided by multiple data partners, in order to actively monitor the safety of approved medical products and answer specific questions.^{34,41} For example, this system showed that bleeding rates associated with the anticoagulant dabigatran were not significantly higher than those associated with warfarin, despite a large number of FAERS reports of serious and fatal bleeding.⁴² Over time, the FDA will continue to enhance the Sentinel System and improve its capabilities, such as broadening data sources beyond those that provide administrative and claims data.³⁴

SAFETY ALERTS

The FDA publicly disseminates MedWatch safety alerts to provide timely new information about drug safety, such as drug recalls, drug-quality issues, and Drug Safety Communications (discussed below), that may affect treatment decisions.⁴³ Also, new FDA-approved labeling changes pertaining

Table 3. Useful Information to Include in a Report Submitted to the FDA Adverse Event Reporting System.

Patient's age and sex
Name of suspected drug, dose, and dates of treatment
Contact information for the person submitting the report
Pertinent patient medical history, including family history
Concomitant medications
Details about the adverse event
Time of adverse event relative to the start of drug treatment
Duration of the adverse event
Risk factors for the adverse event
Treatment, clinical course, and outcome of the adverse event
Results of a positive dechallenge, if performed (i.e., Did the event resolve when the drug was discontinued?)
Results of a positive rechallenge, if performed (i.e., Did the event recur when the drug was restarted?)
Details from the workup for other potential causes of the adverse event, if performed
Details of actual abnormal laboratory or diagnostic results over time, as well as the timing of these abnormal results relative to the use of the drug and concomitant medications

to drug safety are available in real time through the Drug Safety Labeling Changes database.⁴⁴ Anyone can sign up to receive these alerts through the FDA website.^{35,44}

DRUG SAFETY COMMUNICATIONS

The FDA uses Drug Safety Communications to publicly disseminate information about important safety issues affecting FDA-approved drugs.⁴⁵ A Drug Safety Communication describes the safety issue, the drug's approved uses, recommended actions for health care providers and patients, and a summary of the safety data that the FDA has reviewed or is reviewing, as well as any regulatory action taken. From January 2015 through March 2016, the FDA issued 32 Drug Safety Communications, and the home page of

the Drug Safety Communications website received more than 1 million page views. Drug Safety Communications are disseminated through various channels, including FDA Listservs, social and traditional media, and targeted outreach to health care providers. If a drug poses an immediate danger to public health, the FDA uses other communication tools, such as statements, press releases, and media briefings.

CHALLENGES AND FUTURE DIRECTIONS

Many of the FDA's benefit–risk assessments and decisions are straightforward, but sometimes the FDA is confronted with a difficult set of benefits, risks, and uncertainties. Particularly in these situations, the FDA and the drug company may reach different conclusions based on the same facts, or there may be differences of opinion among the members of the FDA's review team. The FDA encourages transparent, robust scientific discussions among its staff and has processes for handling differences of opinion.⁴⁶ There is also a process for drug companies to appeal an FDA decision.⁴⁷ Such situations can be highly charged and can elicit strong public reactions,⁴⁸ with some people criticizing the FDA for being too conservative and delaying access to new drugs, and others criticizing the FDA for being too lenient and approving drugs on the basis of limited data. We believe that the new structured framework for benefit–risk assessment¹³ will facilitate a better understanding of the data and uncertainties underlying drug approvals and will make this information more transparent to the public.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

We thank Eric Brodsky, M.D., Suranjan De, M.S., M.B.A., Neha Gada, Pharm.D., S. Christopher Jones, Pharm.D., M.P.H., Cynthia LaCivita, Pharm.D., David Moeny, R.Ph., M.P.H., John Peters, M.D., Scott Proestel, M.D., and Ann Marie Trentacosti, M.D., for their critical review of an earlier version of the manuscript, and Anne Pariser, M.D., for data analyses.

REFERENCES

1. Total number of retail prescription drugs filled at pharmacies. Menlo Park, CA: Henry J. Kaiser Family Foundation, 2015 (<http://kff.org/other/state-indicator/total-retail-rx-drugs/>).
2. About the Center for Drug Evaluation and Research. Silver Spring, MD: Food and Drug Administration, December 9, 2014 (<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/>).
3. Academic-industry partnerships for biopharmaceutical research & development: advancing medical science in the U.S. Boston: Tufts University School of Medicine (http://csdd.tufts.edu/files/uploads/tuftscsdd_academic-industry.pdf).
4. Development & approval process (drugs). Silver Spring, MD: Food and Drug Administration, January 29, 2016 (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm>).
5. Postmarket drug safety information for patients and providers. Silver Spring, MD: Food and Drug Administration, September 1, 2016 (<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafety>).

- InformationforPatientsandProviders/default.htm).
6. Milestones in U.S. food and drug law history. Silver Spring, MD: Food and Drug Administration, May 14, 2009 (<http://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/default.htm>).
 7. 21 CFR 314.126.
 8. Guidance for industry: providing clinical evidence of effectiveness for human drug and biological products. Silver Spring, MD: Food and Drug Administration, May 1998 (<http://www.fda.gov/downloads/Drugs/GuidanceCompliance%20RegulatoryInformation/Guidances/UCM078749.pdf>).
 9. Quantum of effectiveness evidence in FDA's approval of orphan drugs. Washington, DC: National Organization for Rare Disorders (<http://nordphysicianguides.org/wp-content/uploads/2012/02/NORD-study-of-FDA-approval-of-orphan-drugs.pdf>).
 10. Sasinowski FJ, Panico EB, Valentine JE. Quantum of effectiveness evidence in FDA's approval of orphan drugs update, July 2010 to June 2014. *Ther Innov Regul Sci* 2015;49:680-97.
 11. Downing NS, Aminawung JA, Shah ND, Krumholz HM, Ross JS. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005-2012. *JAMA* 2014;311:368-77.
 12. Drugs@FDA database. Silver Spring, MD: Food and Drug Administration (<https://www.accessdata.fda.gov/scripts/cder/daf/>).
 13. Enhancing benefit-risk assessment in regulatory decision-making. Silver Spring, MD: Food and Drug Administration, July 7, 2015 (<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>).
 14. Rothwell PM. External validity of randomised controlled trials: "to whom do the results of this trial apply?" *Lancet* 2005;365:82-93.
 15. Advisory committees. Silver Spring, MD: Food and Drug Administration, September 2, 2016 (<http://www.fda.gov/AdvisoryCommittees/>).
 16. Smith JF, Townsend SA, Singh N, Ma P. FDA advisory committee meeting outcomes. *Nat Rev Drug Discov* 2012;11:513-4.
 17. Drug applications and Current Good Manufacturing Practice (CGMP) regulations. Silver Spring, MD: Food and Drug Administration, December 17, 2014 (<http://www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm090016.htm>).
 18. New drugs at FDA: CDER's new molecular entities and new therapeutic biological products. Silver Spring, MD: Food and Drug Administration, February 8, 2016 (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm20025676.htm>).
 19. CDER 21st century review process: desk reference guide. Silver Spring, MD: Food and Drug Administration (<http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/manualofpoliciesprocedures/ucm218757.pdf>).
 20. Sacks LV, Shamsuddin HH, Yasinska ya YI, Bouri K, Lanthier ML, Sherman RE. Scientific and regulatory reasons for delay and denial of FDA approval of initial applications for new drugs, 2000-2012. *JAMA* 2014;311:378-84.
 21. Generic Pharmaceutical Association. Generic drug savings in the U.S. — seventh annual edition: 2015 (http://www.gphaonline.org/media/wysiwyg/PDF/GPhA_Savings_Report_2015.pdf).
 22. Understanding generic drugs. Silver Spring, MD: Food and Drug Administration, September 1, 2016 (<http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/understandinggenericdrugs/default.htm>).
 23. Product-specific recommendations for generic drug development. Silver Spring, MD: Food and Drug Administration, August 29, 2016 (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm>).
 24. 21 CFR 201.56(a).
 25. Guidance for industry: safety labeling changes — implementation of Section 505(o)(4) of the FD&C Act. Silver Spring, MD: Food and Drug Administration, July 2013 (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm250783.pdf>).
 26. Safety labeling change orders. Silver Spring, MD: Food and Drug Administration, April 10, 2010 (<http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm189280.htm>).
 27. PLR requirements for prescribing information. Silver Spring, MD: Food and Drug Administration, September 1, 2016 (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>).
 28. FDA basics webinar: a brief overview of Risk Evaluation and Mitigation Strategies (REMS). Silver Spring, MD: Food and Drug Administration, September 2, 2016 (<http://www.fda.gov/AboutFDA/Transparency/Basics/ucm325201.htm>).
 29. Medication guides. Silver Spring, MD: Food and Drug Administration, July 26, 2016 (<http://www.fda.gov/drugs/drugsafety/ucm085729.htm>).
 30. Approved Risk Evaluation and Mitigation Strategies (REMS). Silver Spring, MD: Food and Drug Administration (<http://www.accessdata.fda.gov/scripts/cder/rem/s/>).
 31. 21 CFR part 208.
 32. Staffa JA, Dal Pan GJ. Regulatory innovation in postmarketing risk assessment and management. *Clin Pharmacol Ther* 2012;91:555-7.
 33. Questions and answers on FDA's Adverse Event Reporting System (FAERS). Silver Spring, MD: Food and Drug Administration, May 5, 2016 (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>).
 34. Ball R, Robb M, Anderson SA, Dal Pan G. The FDA's Sentinel Initiative — a comprehensive approach to medical product surveillance. *Clin Pharmacol Ther* 2016;99:265-8.
 35. MedWatch: the FDA safety information and adverse event reporting program. Silver Spring, MD: Food and Drug Administration, September 1, 2016 (<http://www.fda.gov/Safety/MedWatch/>).
 36. Food and Drug Administration. Post-market reviews — topical testosterone gel products: reports of secondary exposure of children to testosterone gel products (marketed as AndroGel 1% and Testim 1%). *Drug Saf News* 2009;2(3):21-3 (<http://www.fda.gov/downloads/drugs/drugsafety/drugsafetynewsletter/ucm192395.pdf>).
 37. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J Clin Epidemiol* 2005;58:323-37.
 38. Guidance for industry and FDA staff: best practices for conducting and reporting pharmacoepidemiologic safety studies using electronic healthcare data. Silver Spring, MD: Food and Drug Administration, May 2013 (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm243537.pdf>).
 39. FDA drug safety communication: azithromycin (Zithromax or Zmax) and the risk of potentially fatal heart rhythms. Silver Spring, MD: Food and Drug Administration, March 12, 2003 (<http://www.fda.gov/Drugs/DrugSafety/ucm341822.htm>).
 40. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012;366:1881-90.
 41. FDA's Sentinel Initiative — background. Silver Spring, MD: Food and Drug Administration, June 27, 2016 (<http://www.fda.gov/Safety/FDA'sSentinelInitiative/ucm149340.htm>).
 42. Ross Southworth M, Reichman ME, Unger EF. Dabigatran and postmarketing reports of bleeding. *N Engl J Med* 2013;368:1272-4.
 43. MedWatch safety alerts for human medical products. Silver Spring, MD: Food and Drug Administration, April 16, 2016 (<http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/>).
 44. Drug Safety Labeling Changes (SLC) database. Silver Spring, MD: Food and Drug Administration, January 19, 2017 (http://www.accessdata.fda.gov/scripts/cder/safetylabelingchanges/?source=govdelivery&utm_medium=email&utm_source=govdelivery).
 45. Drug safety communications. Silver Spring, MD: Food and Drug Administration,

tion, August 31, 2016 (<http://www.fda.gov/Drugs/DrugSafety/ucm199082.htm>).

46. Manual of policies and procedures — resolution of differing professional opinions: review by ad hoc panel and CDER director. Silver Spring, MD: Food and Drug Administration, September 16, 2010

(<http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/ManualofPoliciesProcedures/ucm073558.pdf>).

47. Guidance for industry and review staff — formal dispute resolution: appeals above the division level. Silver Spring, MD: Food and Drug Administration, September 2015 (<http://www.fda.gov/downloads/drugs/>

[guidancecomplianceregulatoryinformation/guidances/ucm343101.pdf](http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm343101.pdf)).

48. Joffe HV, Chang C, Sewell C, et al. FDA approval of flibanserin — treating hypoactive sexual desire disorder. *N Engl J Med* 2016;374:101-4.

Copyright © 2017 Massachusetts Medical Society.



Bald Eagle Staring

Martin Freeman, M.D.