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FDA Policy and Cardiovascular Medicine

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The U.S. Food and Drug Administration (FDA) is among the oldest agencies within the federal government. Its origins can be traced back to 1862, when President Abraham Lincoln appointed a chemist, Charles M. Wetherill, to serve in the Department of Agriculture.[1] One of the key early pieces of legislation that initiated the evolution of the FDA into its modern form was the 1906 Pure Food and Drug Act, which prohibited interstate commerce in misbranded drugs, thereby giving the FDA its first regulatory oversight over medical product labeling.[2] The transformation of the FDA took another major step forward in 1938 with passage of the Food, Drug and Cosmetic Act, which gave FDA authority to require evidence of safety before new drugs could be marketed.[3] Finally, in the 1962 Kefauver-Harris Amendments, the FDA's drug regulatory authority was expanded to require the FDA to certify drug efficacy as well as safety before marketing.[4] The Medical Device Amendments in 1976 gave the FDA similar authority to certify the effectiveness and safety of high-risk medical devices before their approval.[5]

Each of these points in the FDA's early history represented a broadening of its authority and occurred in the context of public health crises related to widely promoted unsafe or ineffective drugs or medical devices, justifying the need for greater government oversight. For example, the Kefauver-Harris Amendments were designed to address the proliferation of medications with poorly documented efficacy and the occurrence of severe and unanticipated side effects caused by some drugs, the most noteworthy example of which was the sedative-antinauseant thalidomide.[6, 7] The 1976 legislation was passed after more than a hundred deaths of young women from a widely promoted, but largely untested, implantable intrauterine contraceptive device.[8] Currently, the FDA describes its responsibilities as assuring the safety, efficacy and security of the medical products for which it maintains

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oversight; advancing the public health by helping to speed innovations that make medicines more effective and safer; and helping the public get the accurate, science-based information they need to use medicines and foods to maintain and improve their health.[9]

Given the FDA's central role in regulating and facilitating access to the medical products that make up physicians' therapeutic armamentarium, it is important that physicians be familiar with the processes and decisions made during drug and device development and evaluation. The purpose of this review is to discuss current FDA policies related to the approval and post-market surveillance of new drug and biologic therapies, generic drugs, and medical devices, along with the implications of these policies for clinical care, particularly in the context of cardiovascular care.

New Drug and Biologic Approval Process

There are essentially 3 phases to the development process for most new therapeutic drugs and biologics: 1) pre-clinical; 2) clinical; and 3) FDA review. The pre-clinical phase involves assessments of safety, and sometimes efficacy, of a potential drug candidate in laboratory and animal models. When it becomes clear that the drug is not toxic to animals, the sponsor must submit an Investigational New Drug (IND) Application to the FDA before human trials can begin. IND applications provide a comprehensive summary of results from animal testing, compound manufacturing and composition information, and describe planned clinical protocols and investigator information for human testing. In allowing an IND to proceed, the FDA makes a determination that human subjects will not be placed at unreasonable risk of harm during clinical testing.

Human clinical testing has traditionally been divided into three phases. Phase I trials are focused on drug safety and typically enroll up to a few dozen healthy volunteers. The primary objective of these dose-ranging studies is to demonstrate safety in humans, and assess the pharmacokinetic and pharmacodynamic properties of the drug, such as half-life, metabolism, and excretion. Phase II trials typically enroll up to a few dozen to a hundred patients, generating the first safety data in patients who have the disease or condition for which the drug is indicated, and may provide preliminary insight into the efficacy of the drug that can be used to plan subsequent trials. Phase III trials provide the first comparative testing of drug efficacy and safety and may enroll hundreds to thousands of patients with the disease or condition of interest. Higher-quality Phase III trials are blinded and randomized, utilize a comparator, and test clinical endpoints (*e.g.*, mortality, hospitalization, relief of symptoms), as opposed to surrogate markers of disease activity (*e.g.*, systolic blood pressure, glycosylated hemoglobin level, tumor progression).

At the completion of clinical trial testing, the manufacturer submits a formal application for approval, seeking FDA approval for marketing in the U.S. This application includes all human and animal studies, as well as information on clinical pharmacology, toxicology, microbiology, chemistry, and manufacturing. The FDA reviews the dossier to assess if there is substantial evidence of efficacy based on "adequate and well-controlled investigations", as well as adequate evidence of safety, and makes a determination as to whether the drug's benefits outweigh risks. The FDA also reviews the manufacturer's planned product labeling,

and makes a decision to approve the NDA or request additional information from the manufacturer. The FDA also normally inspects the facilities where the drug will be manufactured.

What defines "adequate and well-controlled investigations" remains controversial.[10] FDA guidance suggests that two Phase III trials are preferred, each providing independent evidence of efficacy – such studies are known as "pivotal" efficacy trials – but also provides flexibility, describing circumstances in which a single efficacy trial might be sufficient to support approval.[11] Legislation in 2007 formally mandated that the FDA allow drug approval on the basis of a single adequate and well-controlled trial in appropriate cases.[12] Research examining pivotal efficacy trials of new drug and biologics approved from 2005 through 2012 found wide variations in the quality of clinical trial evidence that served as the basis of FDA approval.[13] Over one-third of indications were approved on the basis of a single pivotal efficacy trial. In addition, only 40% were supported by at least one trial that used an active agent as a comparator (as opposed to placebo or no comparator) and 45% were approved on the basis of trials that were exclusively focused on surrogate markers of disease activity. Similarly, fewer than half of new drugs expected to be used for life-long, chronic treatment were supported by at least one trial of 6 months or longer. Among the 23 new drugs approved during this period for treatment of cardiovascular disease, the use of surrogate markers of disease activity was higher than for all non-cardiovascular disease drug approvals. These approval decisions influence clinical care. For example, several drugs that effectively lower low-density lipoprotein cholesterol, including ezetimibe, fenofibrate, and niacin, are now used among large numbers of the population, at great expense, based only on evidence from trials focused on surrogate markers and without clinical trial evidence of their effectiveness for lowering risk of clinical endpoints, such as death or myocardial infarction.[14–17]

When a drug is approved via a New Drug Application, it receives 5 years of guaranteed market exclusivity, during which time no generic versions of the product can be introduced in the market. This is commonly called the "regulatory exclusivity" period, and it is extended to 7.5 years for nearly all new drugs when potential generic drug entrants bring legal challenges to enter the market (see Generic Drug section, below). In practice, drug patents maintain "effective market exclusivity" for new small molecule drugs of about 12–14 years before competition by generic drugs.[18] As will be discussed in more detail later, most biologic drugs (which are approved via Biologics License Applications) enjoyed indefinite protection from generic competition until recently, because there were no clear pathways for approval of follow-on biologic drugs.

Important Features and Variations of the New Drug Approval Processes

Prescription Drug User Fees

The Prescription Drug User Fee Act (PDUFA) was passed in 1992 and authorized the FDA to collect fees from manufacturers submitting new drugs for approval to supplement direct appropriations from Congress. These user fees were enacted at a time when there was widespread dissatisfaction among consumers, industry, and the FDA that the drug approval process was taking too long and that Congressional appropriations to the FDA were too

small, although there is evidence that these appropriations had been growing in the years preceding PDUFA.[19] Initially, the user fees were only allowed to support the review of applications and other industry submissions to the agency, but legislation in 2007 allowed some of the funds to also support post-market safety surveillance activity. User fees now constitute more than $2 billion of the FDA's $4.5 billion total annual budget.[20] As a quid pro quo, the legislation imposed regulatory performance review deadlines on the FDA, such as review of 95% of priority drug applications within 6 months and 95% of standard drug applications within 12 months (shortened to 10 months in 2002). PDUFA requires, and has received, Congressional re-authorization every 5 years since its creation.

After PDUFA was enacted, review times quickly fell from the pre-PDUFA average of 30 months, and there was a spike in new drug approvals after 1992 from the pre-PDUFA back log that had built up.[21] Annual drug approvals subsequently returned to their historic mean,[22] although there has been an uptick in new approvals in the past three years. Currently, the FDA's approval times are the shortest among regulators worldwide. The average FDA regulatory review time for all new drugs and biologics approved from 2001 through 2010 was approximately 10 months, while the regulatory review times at the European Medicines Agency and Health Canada were each approximately 12 months.[23] However, there is evidence that imposing arbitrary regulatory review deadlines on the FDA may pose a risk to public health. Research has found that the PDUFA requirements concentrated the number of approval decisions made in the weeks immediately preceding the deadline and that, as compared with drugs approved at other times, drugs approved in the 2 months before their PDUFA deadlines were significantly more likely than drugs approved at other times to be later found to have important safety risks or to be withdrawn from the market for safety-related reasons.[24] Furthermore, others have raised ethical concerns that the user-fee system, whereby nearly half the FDA's budget is derived directly from manufacturers' payments, beholds the agency to the industry it regulates.[20]

Orphan Drugs

The Orphan Drug Act was enacted in 1983 by Congress to encourage development of new drugs for rare diseases likely to otherwise languish in development because they were anticipated to produce low revenues for manufacturers; in 1984, the definition of a "rare disease" was extended to include conditions that affect fewer than 200,000 patients per year in the U.S. Manufacturers apply for orphan drug designation from the FDA during the clinical phase of drug development. If granted, the designation provides a 7 year regulatory exclusivity period starting at the time of approval, recusal from certain FDA fees, and additional tax breaks for the manufacturer's clinical trials. The orphan drug designation does not formally change the FDA's standard for approval, but in practice, orphan drugs are more likely than drugs for non-rare diseases to be approved on the basis of Phase I and II trials alone or on the basis of trials that use non-randomized, unblinded designs and that test surrogate markers of disease.[13, 25] As would be expected, drugs for rare diseases are also tested in fewer patients overall, with a third as many patients enrolled in pivotal trials for new orphan drugs as for other new drugs.[13, 25] In 2013, the FDA designated a record 260 applications as orphan drugs.[26]

Expedited Approval Pathways

Alternative regulatory pathways facilitate more rapid drug approvals in cases of heightened clinical need.[27–29] The first of these, initiated by FDA in 1988 (later codified by Congress in 1997), is called the Fast Track program, and is intended for drugs treating serious conditions that fill unmet medical needs, defined by the FDA as one that is not "addressed adequately by an existing therapy".[30] Manufacturers of fast track drugs are able to meet and communicate more frequently with the FDA to discuss drug development and clinical trial design to ensure collection of appropriate clinical data to support drug approval. The Fast Track program shortens drug development time,[31] likely by allowing approval on the basis of Phase I and Phase II trials, and includes requirements for post-approval confirmatory trials. The anticipated benefits of the program remain controversial, as comparisons to better understand drug development time and success have been described as challenging.[32]

In 1992, the Accelerated Approval program was initiated for new drugs for serious conditions that fill unmet medical needs, as defined above. Manufacturers of accelerated approval drugs are given special permission by FDA to focus their clinical trial programs on surrogate markers of disease, rather than clinical endpoints, and also must conduct confirmatory post-approval studies. While surrogate markers are expected to be good proxies for clinical benefit, a number of concerns have been raised about their reliability and clinical validity,[33, 34] potentially increasing patient and physician uncertainty about the benefits of new drugs approved through this program.[35] Experience with the accelerated approval program has been studied only occasionally. One review of cancer drugs found that confirmatory evidence of safety and efficacy was eventually developed after approval for only 26 of 47 (55%) new drug indications, among which 3 were removed from the market when post-approval studies found no benefit; trials for the remaining 18 had not yet been completed at the time of the review.[36] Few cardiovascular drugs have received accelerated approval. Midodrine, an α_1-adrenergic agonist, was granted accelerated approval for treatment of symptomatic orthostatic hypotension in 1996; as of August 2010, none of the post-marketing studies required by the FDA to demonstrate clinical efficacy had been completed and the FDA proposed withdrawing the medication, a decision later overturned after protests from patients and clinicians.[37] It remains unclear whether trials have since been completed.[38]

The latest effort by Congress to facilitate more rapid drug approvals by the FDA was the Breakthrough Therapy designation, introduced in 2012. Eligible drugs must be used to treat serious conditions and must have preliminary clinical evidence demonstrating potential for real improvement over standard of care. Though the designation does not formally change the FDA's standard for review, a breakthrough therapy can be approved based on abbreviated or combined traditional clinical phases. For example, the legislation seems to permit designation based on "an effect on a pharmacodynamic biomarker(s) that does not meet criteria for an acceptable surrogate endpoint."[29] This will naturally limit the evidence available to inform patient and physician decisions about these new drug therapies at the time of their FDA approval. Experience with drugs approved under the Breakthrough Therapy designation is just beginning and includes such widely-lauded drugs as sofosbuvir (Sovaldi) for Hepatitis C and supplemental indications for the cystic fibrosis drug ivacaftor

(Kalydeco); thus far the only cardiovascular drug receiving this designation is AAV1/SERCA2a (Mydicar), a genetically targeted enzyme replacement therapy for heart failure patients. Approximately 50 other investigational drugs have been tagged with this designation. Over the past 20 years, these alternative expedited approval pathways have become the norm, rather than the exception. Approximately half of new drug and biologics approved for use in the past decade utilized one or more of pathways intended to make therapeutically important drugs available at an earlier time, and that fraction appears to be rising.[13, 28, 29, 39].

Generic Drug Approval Process

Once a brand-name drug's regulatory- and patent-based market exclusivities end, generic manufacturers of the product may enter the market. Generic drugs are identical to brand-name drugs in dosage form, route of administration, and intended use.[40–42] Generic drugs may differ in superficial features, such as pill color or shape, as well as inactive ingredients.[43, 44] Until 1984, the generic drug market was limited, because the FDA required most generic manufacturers to provide full demonstration of safety and efficacy, similar to brand-name drug approvals. Because of the time and expense required to conduct clinical trials, among 150 brand-name drugs approved after 1962 for which patent exclusivity protections had concluded, generic versions were available on the market for only 15.[45]

In 1984, Congress passed the Drug Price Competition and Patent Term Restoration ("Hatch-Waxman") Act, which allowed the FDA to approve generic drugs on the basis of bioequivalence, or the determination of no significant difference in the availability or absorption of the active ingredient at the site of drug action. Generic manufacturers still must satisfy other regulatory requirements, including labeling, pharmacology/toxicology, chemistry, manufacturing, and inspection. Because research and development costs of generic drugs are far lower than for brand-name drugs, and because there is competition among bioequivalent generic drug manufacturers, generic drug prices are much less than the prices of brand-name drugs.[46] Substitution of low-cost generic drugs has saved consumers over a trillion dollars in the last decade alone.[47] Moreover, there are clear clinical care benefits to generic drug use as their low cost is associated with improved patient adherence when compared with brand-name drugs.[48] A recent study comparing efficacy of generic and brand-name statins found improved clinical outcomes among generic statin users, likely in part because of improved adherence to the lower cost therapy.[49]

In addition, despite generic drugs being cheaper, they remain equally effective. One systematic review and meta-analysis identified 38 head-to-head randomized controlled trials that compared generic and brand-name cardiovascular drugs' clinical efficacy among nine subclasses of medications, the vast majority of which were conducted during the 1980s and 1990s.[50] Clinical equivalence was demonstrated for 35 (92%) of these comparisons, with only 1 of 11 comparisons of diuretic therapies not finding equivalence and 2 of 7 comparisons of calcium channel blockers.[50] Currently, over 8 in 10 prescriptions filled in the U.S. are for generic drugs,[41] and this rate is likely higher for commonly prescribed cardiovascular medications such as cholesterol-lowering statins.[51] Widespread use of generic drugs occurs, in part, because of state pharmacy laws that promote generic drug use

by allowing substitution of FDA-approved generic drugs when a physician writes a prescription for a brand-name drug.[52] Nearly all states also allow patients or the prescribing physician to request the brand-name formulation, although their health insurers may charge more for this choice.[53]

Notable Features of the Generic Drug Market

Barriers to Generic Competition

Brand-name manufacturers use many strategies to delay generic competition as long as possible—a practice called "life-cycle management"—and it would be impossible to review all of those strategies here.[54] One of the most common of such strategies relies on the fact that all pharmaceutical manufacturers frequently patent peripheral aspects of their approved drug products, including metabolites, alternative crystalline structures, or the coating of the pill, and use these later-issued patents to block generic approval even after the patent on the original active ingredient has expired. The Hatch-Waxman Act included an incentive to encourage generic manufacturers to design around and challenge brand-name manufacturers patents in court, reducing the chance that these secondary patents would excessively extend brand-name market exclusivity. That legislation provided a 180-day period of *generic* market exclusivity for the first manufacturer mounting a successful challenge that leads to generic drug approval, essentially creating a duopoly that would artificially inflate generic prices for that period.

In the past decade, many of these Hatch-Waxman patent challenge cases have ended in settlements between the brand-name and generic manufacturers. Some of those settlements have come under scrutiny by the Federal Trade Commission (FTC) because they involved massive payments from the brand-name company to the generic company in exchange for dropping its patent challenge and consequently delaying marketing of its generic drug until a date closer to the end of the patent term. These payments look like anti-competitive business deals between the two companies and have been referred to as "pay for delay" deals.[55] Annual reports by the FTC indicate that generic versions of as many as 142 brand-name drugs have been delayed by pay-for-delay arrangements between drug manufacturers since 2005 and that these arrangements are expected to lead to $35 billion in excess drug spending over the 2010–2020 period.[56] A focused review of the top 20 of these drugs - including well known cardiovascular therapies such as aspirin and extended-release dipyridamole (Aggrenox), amlodipine/atorvastatin (Caduet), atorvastatin (Lipitor) and extended-release niacin (Niaspan) - found that these agreements delayed generic drugs for five years, on average, and for as long as nine years, during which time the brand-name drug companies made an estimated $98 billion in sales.[57] In 2013, the Supreme Court ruled that settlements involving payments can be challenged by the FTC, although whether a particular settlement is actually anti-competitive will be determined by the circumstances of the case.[58].

Biosimilar Approval

The foregoing discussion of the generic drug approval process has applied only to so-called "small-molecule" drugs, in part because the Hatch-Waxman Act did not apply to most biologic drugs. Biologics drugs are large protein therapeutics, such as monoclonal antibodies

or enzymes, usually made from living cells. There was no pathway for approval of follow-on versions of biologic drugs in the U.S. until 2009, when Congress passed the Biologics Price Competition and Innovation Act, one of many components of the Patient Protection and Affordable Care Act.[59] In Europe and other places where follow-on biologics (also called "biosimilars") for a select few products have been available since the mid-2000s, these products have led to 25–30% reductions in drug prices.[60] One of the primary concerns has been that biologics are much more complex than small-molecule drugs and it is still an open question as to whether biologics produced by different manufacturers, but not subject to the same clinical testing, can be confirmed to have similar efficacy or be substituted in routine patient care without causing immunologic or unexpected side effects. The Act gives the FDA the option of approving follow-on biologics as interchangeable or non-interchangeable, and the pre-clinical testing required of follow-on biologics will be more extensive than that for small-molecule generics and will be based on the type of biologic drug.[61] In July 2014, Sandoz announced that it had filed the first-ever biosimilar application for the granulocyte colony-stimulating factor filgrastim (Neupogen),[62] and Celltrion subsequently filed an application for a follow-on version of the tumor necrosis factor-blocking agent infliximab (Remicade). Follow-on versions of epoetin alfa (Epogen) are available throughout Europe and should soon be available in the U.S.

Generic Drug User Fees

Under the Generic Drug User Fee Amendments (GDUFA), introduced in 2012, generic drug manufacturers have for the first time been required to pay user fees, akin to PDUFA. The purpose of these fees is to facilitate the review of the large back-log of generic drug applications that had developed, and provide additional funding to FDA for inspections of generic-drug manufacturing facilities, particularly overseas. Initially, several factors complicated GDUFA implementation, including slower-than-expected registration by generic manufacturers and difficulty knowing which overseas facilities need to register.[63] Under GDUFA, the FDA's review time commitments are much shorter than the average pre-GDUFA review times for generic drug applications, so there is widespread expectation that generic drug applications will be approved more expeditiously.[64]

Medical Device Approval Process

The Medical Device Amendments of 1976 established 2 major pathways through which the FDA could review novel medical devices: Pre-Market Approval (PMA) and 510(k) clearance pathways. The pathway through which a device is authorized for marketing depends on the risk associated with its use, the patient population that stands to benefit from the device, and the existence of similar devices on the market.[65] Class I devices are the lowest risk and include products such as bandages, tongue depressors, and walking canes. Class II devices pose moderate/intermediate risk to patients but have established performance standards and include products such as contact lens solutions and hearing aids. While neither Class I nor Class II medical devices are intended to be used in supporting or sustaining human life, several devices that might be interpreted as meeting this criterion, including hip and knee implants, have been classified as Class II. Class III devices are the highest risk and include products such as implantable cardiac pacemakers, stents, and heart valves.

The PMA pathway is intended to evaluate high-risk devices for which there are no commercially distributed precedents. Applications require clinical testing that provide reasonable assurance that the device is safe and effective for its intended use. The FDA reviews the planned product labeling and also conducts manufacturing inspections before clearing the PMA or requesting additional information from the manufacturer. Notably, the strength of the evidence underlying PMAs can vary. In a study examining 78 high-risk cardiovascular devices that received market clearance by the FDA through the PMA pathway from 2000 through 2007, 65% were found to have been approved on the basis of a single trial.[66] Moreover, only 27% of these trials were randomized, 14% blinded, half had a comparison group (one-third of which were historical controls), and nearly 90% of endpoints were focused on surrogate markers of disease.[66]

The 510(k) pathway generally provides clearance of moderate-risk devices. 510(k) clearance does not require clinical trials that demonstrate safety and effectiveness. Instead, the manufacturer must demonstrate that the device is substantially equivalent in materials, purpose, and mechanism of action to another device already on the market, referred to as the predicate device. In fact, the pathway allows the use of multiple predicates, and reports have found devices cleared on the basis of predicates that have been voluntarily recalled.[67] The 510(k) pathway can allow manufacturers to make small improvements on already marketed devices and allow companies with new products to compete with very similar devices without undergoing extensive clinical testing. The pathway has been criticized, including by the Institute of Medicine, which described the pathway as “unable to optimally protect patients.”[68, 69] From 2003 through 2007, 67% of Class III medical devices received market clearance via the 510(k) pathway,[70] as opposed to via the PMA pathway. In the last few years, the FDA has gone through a rigorous process of re-evaluating some 510(k)-cleared devices to ensure devices are appropriately classified based on potential risk. For example, Automated External Defibrillators are Class III devices, many of which received 510(k) clearance. However, in response to thousands of reports of device failure or malfunction, as well as numerous recalls, in March 2013 the FDA issued a proposed order to require PMA pathway clearance for these devices.

Additional Features of the Medical Device Approval Process

Humanitarian Device Exemption Pathway

In 1990, Congress passed the Safe Medical Devices Act, which led to the creation of the Humanitarian Device Exemption (HDE) pathway. The HDE pathway is available only to humanitarian use devices (HUDs), defined as any device intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the U.S. annually. The HDE pathway requirements are similar to a PMA, but HDE applications are exempt from the effectiveness requirements and must only submit sufficient clinical testing for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury and that the probable benefit outweighs any risk. Since manufacturers' research and development costs could exceed market returns for diseases or conditions affecting small patient populations, the HDE pathway can help motivate development of devices for these rare diseases, for which patients may have no other

treatment alternatives. Some commentators have raised concerns that manufacturers may choose to pursue HDE pathway approval for narrow indications, even for devices likely to be used in broader patient populations.[71] For example, two patent foramen ovale occluders received HDE pathway clearance in 2006 for the treatment of patients with recurrent cryptogenic stroke due to presumed paradoxical embolism through a patent foramen ovale and who have failed conventional drug therapy; however, the FDA withdrew their HDE clearance in 2012 when it became clear that the target population for use of the devices exceeded the statuary threshold.[72] Others have raised concerns that follow-up formal confirmatory testing of HDE devices should be performed, as a review of pediatric HDE clearances suggested such testing may not be happening consistently.[73]

PMA Supplement Pathway

High-risk medical devices originally cleared by the FDA through the PMA pathway can be iteratively changed and re-designed and receive more rapid approval in their modified form, without additional clinical effectiveness or safety evidence, through the PMA Supplement pathway. Such supplements may include major or minor design changes as well as routine changes in labeling, materials, or packaging.[74] From 1979–2012, the FDA cleared 77 initial PMA and 5829 supplement PMA applications for cardiac implantable electronic devices, with a median of 50 supplements per initial PMA pathway clearance (interquartile range, 23–87).[75] Nearly all cardiac implantable electronic device models currently used by clinicians received marketing clearance via PMA supplements.[75] At what point multiple device modifications may change the underlying safety or effectiveness profile and require clinical testing is unknown but deserves further consideration.[76]

Medical Device User Fees

Similar to PDUFA and GDUFA, the Medical Device User Fee Act (MDUFA) was enacted in 2002 and authorizes the FDA to collect fees from medical device companies to supplement direct appropriations from Congress to support the review of PMAs, 510(k) clearances, and other industry submissions to the agency. The Act established performance goals for the agency, such as issuing marketing decisions for PMA submissions within either 180 or 320 days, depending on the need for advisory committee input, or for 510(k) submissions within 90 days. MDUFA requires Congressional re-authorization every 5 years, which most recently occurred in 2012. A recent examination of the FDA's medical device review process, including adherence to MDUFA performance goals, found that Class III medical devices approvals required nearly 400 days of FDA review from 2002 through 2007, have lengthened in duration since 2005, and rarely met MDUFA statutory deadlines.[77] However, other reports have found that the time required to bring a new device to market in the U.S. through the FDA is similar, if not shorter, than the time required in the U.K., France, Italy, and Germany, once regulatory and national payer evaluations are taken into consideration.[78]

Brief Summary: Post-Market Surveillance of Drugs, Biologics, and Medical Devices

A great deal is learned about drug and medical device safety once they are being used actively among patients as prescribed by physicians. A key responsibility of the FDA is to monitor the ongoing safety and effectiveness of medical products and to do this, the FDA

has traditionally relied most heavily on post-market surveillance programs that passively aggregate adverse events: the FDA Adverse Event Reporting System (FAERS) for drugs and the Manufacturer and User Facility Device Experience Database (MAUDE) for medical devices. Both are databases that contain information on adverse event reports submitted to the FDA, the vast majority of which are submitted on a voluntary basis by health care professionals, patients, and industry representatives. While the FAERS and MAUDE systems have successfully detected potential safety issues and contributed to benefit-risk re-assessments, passive surveillance systems have clear limitations, including the submission of incomplete, inaccurate, untimely, unverified, or biased data.[79, 80] In addition, the incidence or prevalence of an event cannot be determined from these reporting systems alone due to under-reporting of events and lack of information about frequency of drug or device use.[79, 80]

To supplement the safety information ascertained through these systems, the FDA can also require that manufacturers conduct post-market studies at the time of market approval, also referred to as Phase IV studies. For medical devices, post-approval studies, including clinical trials and product registries, are often required at the time the device is cleared through the PMA and HDE pathways. In addition, post-market surveillance studies, sometimes referred to as 522 studies, can also be required when safety concerns are identified after a medical device is available for use; these studies are generally used for devices that received 510(k) clearance. Approximately half of drug and biologic approvals between 1990 and 2004 included at least one post-market study commitments, three-quarters of which were clinical studies.[81, 82] Similarly, approximately half of PMA and HDE devices approved since 1995 have been subject to at least one FDA-mandated post-approval study. However, problems have been described in the conduct of post-market study commitments, including inability to track completion of studies and communicate ascertained information to the public and health care professionals. As described further below, the FDA has limited authority to enforce these commitments or penalize manufacturers that do not undertake them in a timely manner.[82]

Post-market safety surveillance is particularly salient to the field of cardiology, as thromboembolic events and cardiac arrhythmias are among the most severe drug- or device-related adverse events experienced by patients. In addition, because many of the clinical trials leading to product approval are of short duration and study relatively small numbers of patients, there may not be sufficient observed patient-time of exposure for adverse event risk to be detected in the trials reviewed by the FDA. For example, the cardiovascular risk associated with rofecoxib (Vioxx) was not apparent for several years after drug approval and eventually led to its market withdrawal.[83] Similarly, nearly a decade had passed after the approval of rosiglitazone (Avandia) before the risk of acute myocardial infarction was identified.[84] More recently, dronedarone (Multaq), a drug used to restore sinus rhythm and reduce hospitalization or death in intermittent atrial fibrillation,[85] was found to increase risk of heart failure, stroke, and death from cardiovascular causes in patients with permanent atrial fibrillation.[86] In both the rosiglitazone and dronedarone cases, the safety concerns identified led the FDA to require that the manufacturers initiate Risk Evaluation and Mitigation Strategies (REMS), which included developing medication guides for patients, communication plans for physicians, and elements for safe use, which are certifications or

other controls to direct drug therapy to patients for whom the benefits outweigh the risks.[87] Post-market safety surveillance is perhaps even more critical for cardiovascular devices, since devices can be cleared for marketing without new clinical data through the 510(k) pathway or with limited data of short duration through the PMA pathway, even for implantable devices. For instance, both the Sprint Fidelis and the Riata and Riata ST implantable cardioverter–defibrillator leads were recalled after the manufacturers identified increased risks of lead fracture and failure, respectively.[88, 89].

Recent Changes to Post-Market Surveillance of Drugs, Biologics, and Medical Devices

FDA Amendments Act

A series of highly publicized drug withdrawals in the 2000s, including rofecoxib,[90] prompted a re-examination of the FDA's post-market surveillance system. The Institute of Medicine recommended that the FDA more closely monitor and evaluate the benefits and risks of drug therapies not only prior to their approval but throughout their entire market life.[91] This approach involves the pursuit and active management of emerging knowledge about the benefit-risk balance as products become more widely used by larger numbers of increasingly diverse patients.[92] In 2007, Congress passed the FDA Amendments Act and provided the agency with additional resources to evaluate drug-safety issues and new authorities to require post-market studies. Since 2007, there has been an increasing number of mandated post-marketing studies: 46 in 2008 and 387 as of 2011.[93] Still, post-market studies remain plagued by delays.[93].

Sentinel Initiative

The FDA Amendments Act also required that the FDA work with public, academic, and private entities to develop a data system to obtain information from existing electronic health care data (primarily administrative claims data gathered by insurers and other payers) to proactively assess medical product safety. Through this legislation, the Sentinel Initiative was established and launched as the Mini-Sentinel program in 2008. The program uses a distributed data approach in which data partners retain control over electronic health care data routinely collected via their health care delivery system as a result of normal activities, but execute standardized computer programs to conduct specific analyses and share aggregated results.[94, 95] Mini-Sentinel engages in active surveillance by conducting pre-specified queries using the distributed data network and does not require patients or clinicians to initiate reports to FDA. The program has made substantial strides towards developing data partners, establishing functional processes and methods, and leveraging big data for regulatory science and public health safety.[96] Outstanding issues include how to reconcile differing results from clinical trials and the Mini-Sentinel program. For example, a recent analysis found that the Mini-Sentinel Program query for gastrointestinal tract bleeding risk associated with dabigatran when compared with warfarin found exactly the opposite of results from a meta-analysis of randomized clinical trials.[97]

Unique Device Identifiers

The Mini-Sentinel program is currently best suited for active post-market surveillance of drugs, rather than medical devices, because medical devices cannot be identified using administrative claims. Another key provision of the FDA Amendments Act required the FDA to establish a Unique Device Identification (UDI) System. Beginning in September 2014, labels and packages of Class III medical devices will include UDIs, unique numbers assigned by the manufacturer to a version or model of a device that will confer production-specific information, including the product's lot number, and manufacturing and expiration date. All medical devices should have a UDI as of 2020. The FDA also plans to create a publicly searchable database, called the Global Unique Device Identification Database, which will serve as a reference catalog to understand device background and history.[98]

Summary

Our review of the approval and post-market surveillance of new drug and biologic therapies, generic drugs, and medical devices shows the range of the FDA's authorities and responsibilities and highlights areas of effective regulatory oversight, as well as some important limitations to the FDA's authority with direct implications for patient care. We found that the FDA has numerous pathways that allow rapid authorization of promising new drugs and devices to address unmet medical needs, and generally performs its functions as quickly—if not moreso—than its counterparts in other countries. However, the choice of approval pathway, for both drugs and devices, clearly impacts the evidence generated to support FDA approval, information that should be clearly communicated to patients and physicians. In addition, post-market surveillance remains a challenge, with methodological and resource limitations. As the health care marketplace is confronted with new and innovative medical products, such as mobile health devices, 3D printers, follow-on biologics, targeted gene therapies, and even medical marijuana, it will be important to learn from the FDA's past experiences in designing policies that optimize its ability to protect the public health.

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References

1. U.S. Food and Drug Administration. [Accessed January 7, 2015] FDA Organizational Histories. 2013 Aug. http://www.fda.gov/AboutFDA/WhatWeDo/History/FOrgsHistory/default.htm.
2. Federal Food and Drugs Act, Pub. L. No. 59-384, 34 Stat. 768. 1906
3. Federal Food, Drug, and Cosmetic Act, Pub. L. No. 75-717, 52 Stat. 1040. 1938
4. Drug Amendments Act, Pub. L. No. 87-781, 76 Stat. 780. 1962
5. Medical Device Amendments, Pub. L. No. 94-295, 90 Stat. 539. 1976
6. Avorn J. Learning about the safety of drugs--a half-century of evolution. N Engl J Med. 2011; 365:2151–2153. [PubMed: 22150034]
7. Greene JA, Podolsky SH. Reform, regulation, and pharmaceuticals--the Kefauver-Harris Amendments at 50. N Engl J Med. 2012; 367:1481–1483. [PubMed: 23075174]
8. Garber AM. Modernizing device regulation. N Engl J Med. 2010; 362:1161–1163. [PubMed: 20335575]
9. U.S. Food and Drug Administration. [Accessed January 7, 2015] What We Do. 2014 Aug. http://www.fda.gov/aboutfda/whatwedo/.
10. Bollen M. Generic substitution of pharmaceuticals. Aust Fam Physician. 1994; 23:2254–2255. [PubMed: 7848139]
11. U.S. Food and Drug Administration. [Accessed January 7, 2015] Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products. 1998 May. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078749.pdf.
12. Food and Drug Administration Amendments Act, Pub. L. No. 110-85, 121 Stat. 823. 2007
13. Downing NS, Aminawung JA, Shah ND, Krumholz HM, Ross JS. Clinical trial evidence supporting FDA approval of novel therapeutic agents, 2005–2012. JAMA. 2014; 311:368–377. [PubMed: 24449315]
14. Jackevicius CA, Tu JV, Ross JS, Ko DT, Carreon D, Krumholz HM. Use of fibrates in the United States and Canada. JAMA. 2011; 305:1217–1224. [PubMed: 21427374]
15. Jackevicius CA, Tu JV, Ross JS, Ko DT, Krumholz HM. Use of ezetimibe in the United States and Canada. N Engl J Med. 2008; 358:1819–1828. [PubMed: 18375999]
16. Ross JS, Frazee SG, Garavaglia SB, Levin R, Novshadian H, Jackevicius CA, Stettin G, Krumholz HM. Trends in Use of Ezetimibe After the ENHANCE Trial, 2007 Through 2010. JAMA Intern Med. 2014; 174:1486–1493. [PubMed: 25070672]
17. Jackevicius CA, Tu JV, Ko DT, de Leon N, Krumholz HM. Use of niacin in the United States and Canada. JAMA Intern Med. 2013; 173:1379–1381. [PubMed: 23753308]
18. Grabowski H, Long G, Mortimer R. Recent trends in brand-name and generic drug competition. J Med Econ. 2014; 17:207–214. [PubMed: 24320785]
19. Carpenter D, Chernew M, Smith DG, Fendrick AM. Approval times for new drugs: does the source of funding for FDA staff matter? Health Aff (Project Hope). 2003 Suppl Web Exclusives:W3-618-24.
20. Avorn J. Paying for drug approvals - Who's using whom? N Engl J Med. 2007; 356:1697–1700. [PubMed: 17435083]
21. Cantor DJ. Congressional Research Service Report for Congress: Prescription Drug User Fee Act of 1992: Effects On Bringing New Drugs To Market. 1997 Sep 12. http://www.law.umaryland.edu/marshall/crsreports/crsdocuments/97-838_E.pdf.
22. Munos B. Lessons from 60 years of pharmaceutical innovation. Nat Rev Drug Discov. 2009; 8:959–968. [PubMed: 19949401]
23. Downing NS, Aminawung JA, Shah ND, Braunstein JB, Krumholz HK, Ross JS. Regulatory Review of Novel Therapeutics - Comparison of Three Regulatory Agencies. N Engl J Med. 2012; 366:2284–2293. [PubMed: 22591257]
24. Carpenter D, Zucker EJ, Avorn J. Drug-review deadlines and safety problems. N Engl J Med. 2008; 358:1354–1361. [PubMed: 18367738]

25. Kesselheim AS, Myers JA, Avorn J. Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer. JAMA. 2011; 305:2320–2326. [PubMed: 21642684]
26. Reardon S. Regulators adopt more orphan drugs. Nature. 2014; 508:16–17. [PubMed: 24695293]
27. U.S. Food and Drug Administration. [Accessed January 7, 2015] Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics. 2014 May. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf.
28. U.S. Food and Drug Administration. [Accessed January 7, 2015] For Consumers: Fast Track, Breakthrough Therapy, Accelerated Approval and Priority Review. 2014 May. http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm.
29. Darrow JJ, Avorn J, Kesselheim AS. New FDA breakthrough-drug category--implications for patients. The New England journal of medicine. 2014; 370:1252–1258. [PubMed: 24670173]
30. U.S. Food and Drug Administration. [Accessed January 7, 2015] Guidance for Industry: Available Therapy. 2004 Jul. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126637.pdf.
31. Shulman SR, Kaitin KI. The Prescription Drug User Fee Act of 1992. A 5-year experiment for industry and the FDA. PharmacoEconomics. 1996; 9:121–133. [PubMed: 10160091]
32. Reichert JM, Rochon SL, Zhang BD. A decade of the Fast Track programme. Nat Rev Drug Discov. 2008; 7:885–886. [PubMed: 18948998]
33. Institute of Medicine. Evaluation of biomarkers and surrogate endpoints in chronic disease. Washington, DC: National Academy Press; 2010.
34. Fleming TR, DeMets DL. Surrogate end points in clinical trials: are we being misled? Ann Intern Med. 1996; 125:605–613. [PubMed: 8815760]
35. Fleming TR. Surrogate endpoints and FDA's accelerated approval process. Health Aff (Project Hope). 2005; 24:67–78.
36. Johnson JR, Ning YM, Farrell A, Justice R, Keegan P, Pazdur R. Accelerated approval of oncology products: the food and drug administration experience. J Natl Cancer Inst. 2011; 103:636–644. [PubMed: 21422403]
37. Dhruva SS, Redberg RF. Accelerated approval and possible withdrawal of midodrine. JAMA. 2010; 304:2172–2173. [PubMed: 21081731]
38. U.S. Food and Drug Administration. [Accessed January 7, 2015] Midrodine Information. 2012 Feb. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm225468.htm.
39. U.S. Food and Drug Administration. [Accessed January 7, 2015] FY 2012 Innovative Drug Approvals. 2013 Dec. http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm276385.htm.
40. U.S. Food and Drug Administration. [Accessed January 7, 2015] Understanding Generic Drugs. 2014 Aug. http://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/understandinggenericdrugs/default.htm.
41. U.S. Food and Drug Administration. [Accessed January 7, 2015] Facts about Generic Drugs. 2012 Sep. http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/ucm167991.htm.
42. Dunne S, Shannon B, Dunne C, Cullen W. A review of the differences and similarities between generic drugs and their originator counterparts, including economic benefits associated with usage of generic medicines, using Ireland as a case study. BMC Pharmacol Toxicol. 2013; 14:1. [PubMed: 23289757]
43. Greene JA, Kesselheim AS. Why Do the Same Drugs Look Different? Pills, Trade Dress, and Public Health. N Engl J Med. 2011; 365:83–89. [PubMed: 21732842]
44. McLachlan AJ. Generic medicines literacy - minimising the potential for patient confusion. Med J Aust. 2010; 192:368–369. [PubMed: 20367580]
45. Mossinghoff GJ. Overview of the Hatch-Waxman Act and its impact on the drug development process. Food and Drug Law Journal. 1999; 54:187–194. [PubMed: 11758572]

46. U.S. Food and Drug Administration. [Accessed January 7, 2015] Generic Competition and Drug Prices. 2010 Mar. http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm129385.htm
47. U.S. Government Accountability Office. [Accessed January 7, 2015] Drug pricing: research on savings from generic drug use. 2012 Jan. http://www.gao.gov/assets/590/588064.pdf.
48. Shrank WH, Hoang T, Ettner SL, Glassman PA, Nair K, DeLapp D, Dirstine J, Avorn J, Asch SM. The implications of choice: prescribing generic or preferred pharmaceuticals improves medication adherence for chronic conditions. Arch Intern Med. 2006; 166:332–337. [PubMed: 16476874]
49. Gagne JJ, Choudhry NK, Kesselheim AS, Polinski JM, Hutchins D, Matlin OS, Brennan TA, Avorn J, Shrank WH. Comparative effectiveness of generic and brand-name statins on patient outcomes: a cohort study. Ann Intern Med. 2014; 161:400–407. [PubMed: 25222387]
50. Kesselheim AS, Misono AS, Lee JL, Stedman MR, Brookhart MA, Choudhry NK, Shrank WH. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. JAMA. 2008; 300:2514–2526. [PubMed: 19050195]
51. Jackevicius CA, Chou MM, Ross JS, Shah ND, Krumholz HM. Generic Atorvastatin and Health Care Costs. N Engl J Med. 2012; 366:201–204. [PubMed: 22149736]
52. Shrank WH, Choudhry NK, Agnew-Blais J, Federman AD, Liberman JN, Liu J, Kesselheim AS, Brookhart MA, Fischer MA. State Generic Substitution Laws Can Lower Drug Outlays Under Medicaid. Health Aff. 2010; 29:1383–1390.
53. [Accessed January 7, 2015] Office of the Assistant Secretary for Planning and Evaluation and U.S. Department of Health and Human Services. Expanding the Use of Generic Drugs. 2010 Dec 1. http://aspe.hhs.gov/sp/reports/2010/genericdrugs/ib.shtml.
54. Balton D. Removing Obstacles to Generic Drug Competition. 2009 Jun. http://www.americanprogress.org/issues/regulation/report/2009/06/23/6281/removing-obstacles-to-generic-drug-competition/.
55. Kesselheim AS, Murtagh L, Mello MM. "Pay for delay" settlements of disputes over pharmaceutical patents. N Engl J Med. 2011; 365:1439–1445. [PubMed: 21916635]
56. Leibowitz, J. [Accessed January 7, 2015] “Pay-for-Delay” Settlements in the Pharmaceutical Industry: How Congress Can Stop Anticompetitive Conduct, Protect Consumers= Wallets, and Help Pay for Health Care Reform (The $35 Billion Solution). 2009. http://www.ftc.gov/sites/default/files/documents/public_statements/pay-delay-settlements-pharmaceutical-industry-how-congress-can-stop-anticompetitive-conduct-protect/090623payfordelayspeech.pdf.
57. U.S. PIRG and Community Catalyst. Top Twenty Pay-For-Delay Drugs: How Drug Industry Payoffs Delay Generics, Inflate Prices and Hurt Consumers. 2013 Jul. http://www.uspirg.org/sites/pirg/files/reports/Top_Twenty_Pay_For_Delay_Drugs_USPIRG.pdf.
58. Denniston L. Opinion recap:“Pay to delay” in deep trouble. 2013 http://www.scotusblog.com/2013/06/opinion-recap-pay-to-delay-in-deep-trouble/.
59. Kozlowski S, Woodcock J, Midthun K, Sherman RB. Developing the nation's biosimilars program. N Engl J Med. 2011; 365:385–388. [PubMed: 21812668]
60. U.S. Federal Trade Commission. [Accessed January 7, 2015] Emerging Health Care Issues: Follow-On Biologic Drug Competition: A Federal Trade Commission Report. 2009 Jun. http://www.ftc.gov/reports/emerging-health-care-issues-follow-biologic-drug-competition-federal-trade-commission-report.
61. U.S. Food and Drug Administration. [Accessed January 7, 2015] Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. 2012 Feb. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf.
62. Gaffney A. Sandoz First Company to File for Biosimilar Approval in US Under New Pathway. 2014 Jul. http://www.raps.org/Regulatory-Focus/News/2014/07/24/19818/Sandoz-First-Company-to-File-for-Biosimilar-Approval-in-US-Under-New-Pathway/.
63. Gaffney A. FDA Releases Extensive Final Q&A Guidance on Generic User Fees. 2013 Sep. http://www.raps.org/regulatoryDetail.aspx?id=9407.
64. U.S. Food and Drug Administration. [Accessed January 7, 2015] GDUFA Regulatory Science. 2014 Oct. http://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/ucm370952.htm.

65. U.S. Food and Drug Administration. [Accessed January 7, 2015] How to Market Your Device. 2014 Aug. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/default.htm.
66. Dhruva SS, Bero LA, Redberg RF. Strength of study evidence examined by the FDA in premarket approval of cardiovascular devices. JAMA. 2009; 302:2679–2685. [PubMed: 20040556]
67. Ardaugh BM, Graves SE, Redberg RF. The 510(k) ancestry of a metal-on-metal hip implant. N Engl J Med. 2013; 368:97–100. [PubMed: 23301729]
68. Zuckerman DM, Brown P, Nissen SE. Medical device recalls and the FDA approval process. Arch Intern Med. 2011; 171:1006–1011. [PubMed: 21321283]
69. Institute of Medicine. Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years. Washington, DC: National Academy Press; 2011.
70. U.S. Government Accountability Office. [Accessed January 7, 2015] FDA Should Take Steps to Ensure That High-Risk Device Types Are Approved through the Most Stringent Premarket Review Process. 2009 Jan. http://www.gao.gov/assets/290/284882.pdf.
71. Kaplan AV, Harvey ED, Kuntz RE, Shiran H, Robb JF, Fitzgerald P. Humanitarian Use Devices/Humanitarian Device Exemptions in cardiovascular medicine. Circulation. 2005; 112:2883–2886. [PubMed: 16267261]
72. U.S. Food and Drug Administration. [Accessed January 7, 2015] Information for Physicians and Patients on the Withdrawal of Two Humanitarian Device Exemptions (HDEs) For Patent Foramen Ovale (PFO) Occluders. 2012 Feb. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/ucm135747.htm.
73. Hwang TJ, Kesselheim AS, Bourgeois FT. Postmarketing Trials and Pediatric Device Approvals. Pediatrics. 2014; 133:e1197–e1202. [PubMed: 24733871]
74. U.S. Food and Drug Administration. [Accessed January 7, 2015] Guidance for Industry and FDA Staff: Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process. 2008 Dec. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM089360.pdf.
75. Rome BN, Kramer DB, Kesselheim AS. FDA approval of cardiac implantable electronic devices via original and supplement premarket approval pathways, 1979–2012. JAMA. 2014; 311:385–391. [PubMed: 24449317]
76. Zheng SY, Redberg RF. Premarket approval supplement pathway: do we know what we are getting? Ann Intern Med. 2014; 160:798–799. [PubMed: 24664113]
77. Zinn AM, Allen JC Jr, Hacker CS. Median approval times for class III medical devices have been well above statutory deadlines set for FDA and CMS. Health Aff (Project Hope). 2012; 31:2304–2313.
78. Basu S, Hassenplug JC. Patient access to medical devices--a comparison of U.S. and European review processes. N Engl J Med. 2012; 367:485–488. [PubMed: 22852882]
79. U.S. Food and Drug Administration. [Accessed January 7, 2015] FDA Adverse Event Reporting System (FAERS). 2014 Sep. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm.
80. U.S. Food and Drug Administration. [Accessed January 7, 2015] MAUDE - Manufacturer and User Facility Device Experience. 2014 Jul. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM.
81. U.S. Food and Drug Administration. [Accessed January 7, 2015] Report to Congress: Reports on Postmarketing Studies [FDAMA 130]. 2001 Apr. http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm071529.pdf.
82. U.S. Department of Health and Human Servies and Office of Inspector General. [Accessed January 7, 2015] FDA's Monitoring of Postmarketing Study Commitments. 2006 Jun. http://oig.hhs.gov/oei/reports/oei-01-04-00390.pdf.
83. Ross JS, Madigan D, Hill KP, Egilman DS, Wang Y, Krumholz HM. Pooled analysis of rofecoxib placebo-controlled clinical trial data: lessons for postmarket pharmaceutical safety surveillance. Arch Intern Med. 2009; 169:1976–1985. [PubMed: 19933959]

84. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. N Engl J Med. 2007; 356:2457–2471. [PubMed: 17517853]
85. Hohnloser SH, Crijns HJ, van Eickels M, Gaudin C, Page RL, Torp-Pedersen C, Connolly SJ. Effect of dronedarone on cardiovascular events in atrial fibrillation. N Engl J Med. 2009; 360:668–678. [PubMed: 19213680]
86. Connolly SJ, Camm AJ, Halperin JL, Joyner C, Alings M, Amerena J, Atar D, Avezum A, Blomstrom P, Borggrefe M, Budaj A, Chen SA, Ching CK, Commerford P, Dans A, Davy JM, Delacretaz E, Di Pasquale G, Diaz R, Dorian P, Flaker G, Golitsyn S, Gonzalez-Hermosillo A, Granger CB, Heidbuchel H, Kautzner J, Kim JS, Lanas F, Lewis BS, Merino JL, Morillo C, Murin J, Narasimhan C, Paolasso E, Parkhomenko A, Peters NS, Sim KH, Stiles MK, Tanomsup S, Toivonen L, Tomcsanyi J, Torp-Pedersen C, Tse HF, Vardas P, Vinereanu D, Xavier D, Zhu J, Zhu JR, Baret-Cormel L, Weinling E, Staiger C, Yusuf S, Chrolavicius S, Afzal R, Hohnloser SH. Dronedarone in high-risk permanent atrial fibrillation. N Engl J Med. 2011; 365:2268–2276. [PubMed: 22082198]
87. U.S. Food and Drug Administration. [Accessed January 7, 2015] Approved Risk Evaluation and Mitigation Strategies (REMS). 2015 Jan. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm.
88. Hauser RG. Here we go again--failure of postmarketing device surveillance. N Engl J Med. 2012; 366:873–875. [PubMed: 22332951]
89. Maisel WH. Semper fidelis--consumer protection for patients with implanted medical devices. N Engl J Med. 2008; 358:985–987. [PubMed: 18322280]
90. Krumholz HM, Ross JS, Presler AH, Egilman DS. What have we learnt from Vioxx? BMJ. 2007; 334:120–123. [PubMed: 17235089]
91. Institute of Medicine. The Future of Drug Safety: Promoting and Protecting the Health of the Public. Washington, DC: National Academy Press; 2006.
92. Psaty BM, Meslin EM, Breckenridge A. A lifecycle approach to the evaluation of FDA approval methods and regulatory actions: opportunities provided by a new IOM report. JAMA. 2012; 307:2491–2492. [PubMed: 22563032]
93. Fain K, Daubresse M, Alexander GC. The Food and Drug Administration Amendments Act and postmarketing commitments. JAMA. 2013; 310:202–204. [PubMed: 23839755]
94. Mini-Sentinel. Welcome to Mini-Sentinel. http://www.mini-sentinel.org/default.aspx.
95. Behrman RE, Benner JS, Brown JS, McClellan M, Woodcock J, Platt R. Developing the Sentinel System--a national resource for evidence development. N Engl J Med. 2011; 364:498–499. [PubMed: 21226658]
96. Psaty BM, Breckenridge AM. Mini-Sentinel and regulatory science--big data rendered fit and functional. N Engl J Med. 2014; 370:2165–2167. [PubMed: 24897081]
97. Sipahi I, Celik S, Tozun N. A comparison of results of the US food and drug administration's mini-sentinel program with randomized clinical trials: the case of gastrointestinal tract bleeding with dabigatran. JAMA Intern Med. 2014; 174:150–151. [PubMed: 24247291]
98. Wilensky GR, Redberg RF. Health policy update 2014: another exciting and turbulent year ahead. JAMA Intern Med. 2014; 174:837–838. [PubMed: 24671246]