The US Food and Drug Administration, neurologists, and drug development and regulation

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Summary

The US Food and Drug Administration (FDA) plays a vital role in the regulation of human drugs and therapeutic biologics. Most physicians, while aware of the broad reach of the FDA, are unaware of what the agency actually does and how it does it. Practicing neurologists should be aware of the role neurologists can play in drug development, the informational resources that the FDA provides to practitioners, and the process of submitting reports of suspected adverse drug reactions to the FDA.

The FDA is a science-based, public health-oriented regulatory agency whose purview includes regulation of human drugs and biologics, medical devices, animal drugs and feed, food, and tobacco. The regulation of human drugs and therapeutic biologics has a direct effect on all practicing neurologists.

The FDA's role in drug development

In the past 2 decades, the pharmacologic armamentarium for neurologic diseases has increased substantially. New classes of drugs for epilepsy, immune-based treatments for multiple sclerosis (MS), and novel treatments for Parkinson disease are just a few examples of FDA approvals in the field of neurology in the past 20 years. As basic research unravels the underlying pathophysiology of these diseases, drug discovery seeks to find new—and more effective—treatments for them.

Drug development—the process by which a drug goes through a carefully planned set of animal studies, clinical pharmacology studies, and clinical trials in order to become an

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approved drug—is a highly complex endeavor that can take several years and involves basic scientists, clinical researchers, and regulators (figure). Throughout this process, a multidisciplinary FDA review team composed of chemists, toxicologists, clinical pharmacologists, medical reviewers, statisticians, regulatory project managers, and others may meet with a pharmaceutical company to provide scientific and regulatory input on the company's plans. For example, FDA staff may meet with a pharmaceutical company before human testing is started, at the end of phase 2 (when proof-of-principle and dose-ranging studies have been completed), before submission of the application for approval, and at other times during the development process. Once the company has completed its studies, it submits the results in a New Drug Application or a Biologics License Application, which the FDA multidisciplinary team reviews to determine whether the data support approval. The FDA may also meet with the company during the application review process. The clinical review focuses on characterization of efficacy and safety, and, most importantly, determination of whether or not the benefits of the drug or biologic outweigh its risks. Because such determinations are not always straightforward, the FDA may ask an advisory committee to render an opinion on the drug or biologic before the FDA makes its final decision. For public discussion of new drug approval, the FDA typically convenes an advisory committee in the relevant therapeutic area. If needed, additional advisors or advisory committees join the therapeutic area committee. Advisory committees are composed of clinical and other experts in a particular therapeutic area or other relevant field. For drugs and therapeutic biologics for the treatment of neurologic disease, the FDA's Peripheral and Central Nervous System Advisory Committee,¹ on which several neurologists serve, would discuss the application. Advisory committee meetings are open to the public, and transcripts are available after the meeting. The general process is similar for small molecule drugs and therapeutic biologics. Differences between the development of a small molecule drug and a therapeutic biologic are beyond the scope of this overview.

Neurologists can play an important role in drug development

Neurologists are often involved in many aspects of development of potential new therapies for neurologic diseases. The clinical development of medicines includes rigorous clinical trials, whose design and outcome determine the approved indications. For this reason, neurologists are critical to the design, conduct, and interpretation of clinical trials of neurologic therapeutics. For example, neurologists who are experts in a particular disease may be involved in the development and validation of scales or other instruments that measure the effect of treatment. Clinical experts are also needed to determine the magnitude of a clinically meaningful effect, a crucial factor in the design of a clinical trial. In clinical trials, neurologists can serve as principal investigators, site investigators in multisite clinical trials, members of data safety monitoring boards, or in other capacities. The FDA oversees clinical trials to protect research subjects.

The product label, or package insert, conveys information essential for prescribing the medicine

A new medicine's approved label, also known as the package insert, is what the neurologist can refer to for information essential to prescribing the medicine. Because newly approved medicines typically undergo comprehensive testing prior to approval, there is a substantial body of information that can inform careful prescribing. In 2006, after consultation with physicians, the FDA developed a new format for the label that is designed to provide useful

Figure Drug development and lifecycle timeline

The figure illustrates the principal activities that occur during the lifecycle of a drug, from prehuman studies through postmarketing surveillance. The duration of each phase varies from drug to drug and is not reflected in the figure. FDA = US Food and Drug Administration.

information that is easy to locate.² The package insert, which is developed by the pharmaceutical company and approved by the FDA, describes the drug, indications for use, dosage and administration, dosage forms and strengths, contraindications, warnings and precautions, adverse reactions, drug interactions, use in specific populations, drug abuse and dependence, overdose, clinical pharmacology, nonclinical toxicology, the clinical studies that support approval, and other helpful information, such as patient counseling information. Because knowledge of a drug or biologic's safety continues to be accrued after approval, the package insert may be updated with additional safety information throughout a product's lifecycle. In addition, a company may conduct clinical trials for new indications for the drug or biologic, which, if approved, would be added to the package insert. For these reasons, it is important to refer to the current version of the package insert. The current package insert for a drug can be found at the DailyMed Web site.³

In practice, the actual use of a medicine once it is marketed may deviate from the conditions of use specified in the FDA-approved labeling. Such "off-label" use may occur, for example, when a practitioner prescribes a medicine for an indication for which the FDA has not granted approval, for a population that is not mentioned in the label, or at a dose not mentioned in the label. At times, off-label use of a medicine may become part of accepted medical practice and be included in professional practice guidelines. There may be reasonable published evidence to support off-label use in some cases; in others, such use is speculative. The FDA regulates the marketing of medicines, but it does not regulate prescribing practices.⁴ The FDA's postmarketing drug safety surveillance efforts, described below, focus on both on-label and off-label use. For example, the package insert for the antiepileptic drug tiagabine carries a warning that the drug may cause seizures in people without epilepsy.⁵

Knowledge of a medicine continues to be accrued after approval

Clinical trials that support a drug's approval cannot predict all the individual adverse reactions that may occur once the medicine is widely used in a population of patients who are more heterogeneous than those studied in clinical trials. For this reason, careful postmarket safety monitoring of medicines is necessary.⁶ While postmarketing safety monitoring has evolved over the past 4 decades, the cornerstone has been the voluntary reporting of suspected adverse drug reactions by physicians and others at the point of care either directly to the FDA or to a drug's manufacturer, who is then required to report these suspected adverse drug reactions to the FDA. Often, the first clue that a drug may cause a previously unrecognized adverse

The FDA regulates the marketing of medicines, but it does not regulate prescribing practices.

reaction comes from careful clinical observations made by individual practitioners. While recognition of such a potential association is clearly important for the management of an individual patient, the information can also aid the FDA and the drug's manufacturer in better understanding the safety profile of a drug. These reports are entered into the FDA's Adverse Event Reporting System, which contains about 9 million such reports. Review of individual case safety reports, or other techniques such as data mining, can generate a signal of a potential adverse drug reaction. Once a signal is generated, further investigation is necessary. In some cases, a careful review of detailed case reports can establish a sufficient causal relationship between the drug and the suspected adverse drug reactions. This is especially true for adverse drug reactions that develop shortly after the drug is started, have very low background rates, are usually the result of drug exposure, and are not a manifestation of the disease being treated. Examples of adverse drug reactions in this category are acute liver failure (in the absence of other obvious explanations), aplastic anemia and agranulocytosis (again, in the absence of other obvious causes), and torsades de pointes.

For example, the association between felbamate, an antiepileptic agent approved in July 1993, and aplastic anemia was elucidated through adverse event reports.⁷ Within about 1 year of its approval, 20 cases of aplastic anemia, 3 fatal, had been reported in the United States. Review of the case reports suggested a causal role for felbamate. Based on the number of reports received and the extent of use of felbamate, the FDA concluded that aplastic anemia is about 100 times more frequent in patients taking felbamate than in the general population. Based on this finding, the FDA and the manufacturer recommended that patients not be treated with felbamate unless the benefits of the drug outweighed the risk of aplastic anemia.

In many cases, however, a case report or case series is not sufficient to establish a link between a drug and an adverse reaction because the observed reaction may be a manifestation of the underlying disease or may be common in the treated population. In these cases, observational epidemiologic studies or clinical trials may be needed to sort out the issue. For example, a retrospective cohort study using administrative claims data examined the incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering agents.⁸ This study demonstrated that the rate of hospitalized rhabdomyolysis was higher for cerivastatin than for other statins, including atorvastatin, pravastatin, and simvastatin, and that coadministration of a statin and fibrates increased this risk. In another example, a nested case-control study examining the relationship of dopamine agonists to cardiac valve regurgitation determined that 2 agents, pergolide and cabergoline, were associated with the development of this adverse effect whereas other dopamine agonists, including levodopa, selegiline, bromocriptine, lisuride, pramipexole, and ropinirole, were not.⁹

Neurologists can play an important role in postmarketing drug safety

Neurologists can contribute to the FDA's body of postmarket safety knowledge by reporting suspected adverse drug reactions to the FDA. Practitioners can report a suspected adverse drug reaction directly to the FDA through the MedWatch program or to the manufacturer.^{10,11} This is a critical role that all health care practitioners can play. A high-quality adverse event report need not be lengthy, although it should include sufficient information for an independent reviewer to evaluate the association between the drug and the suspected adverse drug reaction. High-quality reports usually include a description of the event; details of the suspected product(s) and concomitant treatment; patient characteristics; medical history, including treatment history; documentation of the diagnosis of the suspected adverse drug reaction; clinical course and outcomes of the suspected adverse drug reaction; treatment and lab values at

baseline, during therapy, and after therapy; response to dechallenge (withdrawal of the drug) and rechallenge (reintroduction of the drug after the suspected adverse drug reactions had initially abated); and any other relevant information. Approximately one-half of postapproval safety-related changes made to a drug's label are based on adverse event reports. Thus, neurologists should know that they can make a difference by reporting adverse event information to the FDA or to a drug's manufacturer.

Risk evaluation and mitigation strategies

For certain medicines, the FDA, using authorities granted to it by the Food and Drug Administration Amendments Act of 2007, can require the drug or biologic's manufacturer to impose certain conditions or restrictions on the use of medicine. The programs that impose these restrictions are known as risk evaluation and mitigation strategies, or REMS. These programs, which are imposed for very few medicines, are designed to ensure that the benefits of the medicine outweigh its risks when the FDA determines that labeling (i.e., the package insert) alone is not sufficient. The details vary from program to program; when special action is needed on the physician's part, the manufacturer should have a system in place that allows physicians to know what they need to do. For example, to ensure that the benefits of natalizumab for MS outweigh the risk of progressive multifocal leukoencephalopathy (PML), the Tysabri TOUCH program requires that only enrolled physicians prescribe natalizumab, only enrolled patients receive it, only certain authorized pharmacies dispense it, and only certain infusion centers administer it. The enrollment requirements ensure that all parties are aware of the risk of PML and of the factors that can increase that risk and that certain monitoring occurs during treatment with natalizumab.¹² The REMS for vigabatrin also uses certain restrictions to manage the risk of visual loss.¹³ A list of all FDA-approved REMS can be found on the FDA's Web site.¹⁴

Additional information from the FDA can help neurologists in practice

Beyond FDA-approved package inserts, neurologists can find additional information about drug safety on the FDA's Web site. For the past several years, the FDA has been issuing Drug Safety Communications for certain emerging drug safety issues when it has completed an analysis of available data and, in some cases, before it has reached a conclusion that regulatory action is needed.¹⁵ While these communications are issued for a relatively small number of drugs, they can provide useful information that neurologists may want to consider when prescribing a drug.¹⁶ The FDA's MedWatch program maintains a Web site¹⁷ that provides timely new safety information on human drugs, medical devices, vaccines and other biologics, dietary supplements, and cosmetics. Finally, a variety of safety-related drug information can be found on a portion of the FDA Web site dedicated specifically to drug safety.¹⁸

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