ly less attention in FDASIA. Though many experts have called for substantial changes to the postmarketing surveillance of medical devices in particular, reforms specified in the legislation were generally limited to several areas of "program development" — requests for the FDA to develop frameworks, strategies, or processes related to improving postmarketing surveillance and enforcement. For example, the FDA was directed to create a program to evaluate device-recall data with the goal of minimizing the negative impact of recalls on public health; to include medical devices in the current Sentinel program for drugs, an early-stage program aimed at developing data sources and designing methods for identifying signals of safety concerns; and to propose a draft rule, which has now been released, for "unique device identifiers" as a mechanism for better tracking of device-related events.

In the realm of pharmaceutical products, FDASIA aims to help streamline the approval of generic drugs, as well as to ensure the safety of the drug supply and distribution chain. First, the law extends user fees to the manufacturers of generic drugs to provide greater funding for the FDA's generic-drug reviewers and thereby reduce the backlog of applications for the approval of such products. However, the law does not address the strategies that currently prevent approved generic drugs from reaching the market.[4] The legislation also contains provisions aimed at bringing attention to and assuring the safety of the drug supply chain, which has emerged as a growing concern. Currently, 80% of all active ingredients and 40% of drug tablets sold in the United States originate overseas. The FDA has traditionally had limited resources for inspecting non-U.S. facilities, so FDASIA provides directions for more frequent inspections and greater transparency regarding the origins of final products.

Although FDASIA ensures that the FDA will receive the ongoing user-fee funding it needs in the absence of realistic government appropriations and includes new initiatives that may help promote review efficiency, it missed an opportunity to promote more robust postmarketing systems to validate the effectiveness and ensure the safety of marketed products. For example, a greater proportion of user fees might have been directed toward personnel who serve surveillance functions such as analysis and aggregation of adverse-event reports, toward research evaluating novel ways of analyzing postmarketing data, or toward facilitating the development of infrastructure such as targeted registries. Additional provisions might have included more specific penalties for missing postapproval commitments or mechanisms for industry to share postmarketing data currently viewed as proprietary, with the goal of detecting important safety signals. Indeed, when the more efficient premarketing processes for drugs and devices envisioned by FDASIA are implemented, the number of drugs and devices requiring rigorous postapproval surveillance will only increase.

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From Harvard Medical School (D.B.K., A.S.K.), the Cardiovascular Institute, Beth Israel Deaconess Medical Center (D.B.K.), and the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital (A.S.K.) — all in Boston.

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France's New Framework for Regulating Off-Label Drug Use

Joseph Emmerich, M.D., Ph.D., Nathalie Dumarcet, M.D., and Annie Lorence, Pharm.D.

Off-label use of drugs is relatively common in medical practice, even if it's often not supported by strong scientific evidence. Studies in the United States have shown that off-label use may account for approximately 20% of prescriptions, or 150 million prescriptions per year.[1] In addition to its economic effect on the health care system, the inappropriate off-label use of drugs

raises major concerns about safety, especially when a drug is widely used regardless of the fact that regulatory agencies have not determined its benefit–risk ratio. In France, a recent scandal involving Mediator (benfluorex) — a fenfluramine derivative approved for treating diabetes but prescribed for indications (weight loss) not included in the "summary of product characteristics" (label), which caused sometimes-fatal valvular heart disease — paved the way for major changes in the regulatory system, including new measures aimed at strongly regulating access to drugs during their postmarketing "real life."[2]

A major challenge for regulatory agencies is balancing the need for rapid access to drugs for new indications against the limited information on their benefit–risk ratio for those uses.[3] Several approaches to regulating off-label prescribing have been proposed.[4] A recently passed French law aimed at strengthening the safety of medicines and health care products (Law number 2011-2012, December 29, 2011) and a related decree regarding "Temporary Recommendations for Use" (TRUs; Decree number 2012-743, May 9, 2012) fill part of the gap, providing France with a regulatory process for temporarily supervising the prescribing of drugs for indications for which they are not yet licensed.

Marketing authorization for drugs is granted on the basis of their safety for specific indications, as ensured by a positive benefit–risk ratio in clinical studies. To be appropriate and safe, a drug's use should adhere to its summary of product characteristics. Nevertheless, some licensed medicines may be prescribed for indications outside their marketing authorization in order to treat health problems for which there are currently no other approved medications — for instance, in the case of rare diseases or specific subgroups of patients.[5] Some off-label prescribing should be permitted to allow physicians to take good care of patients and offer them some therapeutic options, but such prescriptions must remain the exception to the rule and should be scrutinized and controlled by regulatory agencies using well-defined frameworks.

The intention of the French law and the TRU decree is to open a relatively long observation window in order to assess the benefits and risks of a marketed drug for an unlicensed indication and to collect scientific information to ensure its safe use. A TRU is granted for a maximum of 3 years, a window that should permit the manufacturer to expand its marketing authorization through the usual procedures. Furthermore, the law gives pharmaceutical firms the responsibility for controlling off-label prescribing: they must monitor prescriptions' adherence to marketing authorizations and must not market their drugs for unlicensed indications. If unconventional prescribing is observed, pharmaceutical firms must immediately inform the National Agency of Medicine and Health Product Safety (Agence Nationale de Sécurité du Médicament et des Produits de Santé [ANSM]) and take all appropriate measures to inform health care professionals and prevent off-label use.

A TRU decision is issued a single time for any given drug and may result in a right to reimbursement for the drug for the designated indication. The ANSM will authorize a TRU if there are no other appropriate medications available. The ANSM may be alerted to the possible need for a TRU by the Ministry of Health, the institution in charge of Social Security Insurance, the High Health Authority, the National Cancer Institute, the reference centers for rare diseases, or patient advocacy groups. After the agency assesses the data provided by the manufacturer and from academic scientific studies, it can issue a TRU.

A formal contract may be signed between the company marketing the drug and the ANSM. Such an agreement would define the patient follow-up, the efficacy and safety information to be collected, the real conditions of use, and the schedule for reporting data to the ANSM. The cost of this follow-up must be covered by the pharmaceutical firms, but the follow-up itself can be delegated to specialized organizations or reference centers. This monitoring does not cover other off-label use not included in the TRU. If there is found to be a risk to public health or a lack of follow-up of patients, the ANSM can modify, suspend, or withdraw the TRU.

Several factors must be considered and carefully balanced by an expert committee before a TRU can be issued. The first is the quality of the scientific evidence: as with any medical procedure, such evidence should be the main reason for issuing a TRU for a given indication, and controlled studies will remain the gold standard for this purpose. Although in some cases high-quality epidemiologic studies may support the definition of a TRU,

if only anecdotal evidence or poor-quality studies exist, further clinical trials will have to be conducted so that stronger scientific evidence may be gathered before a TRU can be obtained.

The second factor is the drug's safety. Obviously, it's safer to issue a TRU for a well-known drug with few side effects than for a drug with serious side effects that has been on the market for only a short time. The risk associated with the medication in terms of drug interactions and potential harm in specific populations such as pregnant women, the elderly, or patients with renal insufficiency should also be considered, as should the required duration of treatment.

Third, the prognosis associated with a given disease must be considered: it makes more sense to issue a TRU for a severe disease than for a mild or trivial one. Indeed, regulators as well as caregivers and patients are more willing to accept greater uncertainty regarding the benefit–risk assessment for a life-threatening disease with no alternative treatment. For this reason, TRUs will probably be used most often in oncology and hematology, followed by infectious diseases.

The fourth consideration is the frequency of the disease's occurrence. In some rare diseases or subgroups of patients, it can be challenging to perform large clinical studies to develop evidence supporting new marketing authorizations for drugs. In these cases, a TRU could hasten the conduct of clinical research. In common diseases, randomized trials remain the gold standard for drug development and approval.

The regulatory rules for off-label use warrant strengthening not only in France, but also in the European Union and other countries, to reduce the potential harm to patients. The new French legislation also aims to facilitate and promote the development of new indications, refine benefit–risk assessments for real-life prescribing practices, and avert the loss of therapeutic options for eligible patients. The advantage of TRUs is that they will encourage the development of possibly viable uses for marketed drugs and the monitoring of benefit–risk ratios for new indications. The potential downside is that once a new use has been temporarily authorized, it may be difficult to stop physicians from prescribing the drug for that indication even if new market authorization is not granted.

Nevertheless, we believe that the development of the TRU is a major step forward for public health and paves the way for tighter control of off-label prescribing. We hope that it will also foster the development of new indications for specific subgroups of patients or rare diseases. Like the conditional marketing authorizations that have been issued by the European Medicines Agency's Committee for Medicinal Products for Human Use, the French TRU regulation deserves to be discussed and potentially extended, when suitable, to European Union and other countries and adapted to the organization of their health care systems.

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Unpredictable and Difficult to Control — The Adolescence of West Nile Virus

Lyle R. Petersen, M.D., M.P.H., and Marc Fischer, M.D., M.P.H.

Disturbingly unpredictable, disagreeable, and difficult to control — West Nile virus, first identified in the United States in 1999, has entered adolescence. In this year's tally, 3142 cases of West Nile virus disease in humans in 45 states had been reported to the Centers for Disease Control and Prevention as of September 18, 2012, including 1630 cases of resulting neuroinvasive dis-