

provided FDA with the resources and the tools to fulfil its mission to protect and promote the health of the public. The measure of the FDA leadership in coming years will be the degree to which the newly deployed post-marketing system becomes a model for other drug regulatory authorities.”

The *New York Times* also reported Billy Tauzin, president and CEO of industry association the PhRMA, stating: “The US House of Representatives has taken a crucial step to make our nation’s drug safety system, which already is the best in the world, even better.” Industry publications, meanwhile, have taken a more cautious stance, focusing on the complexities and uncertainties in the Act and the potential for a slowdown in the drug approvals process.

Both the International Society for Pharmacoepidemiology (ISPE) and the International Society For Pharmacoeconomics and Outcomes Research (ISPOR) included panel discussions on the FDAAA during their Spring 2008 meetings. In both cases, panellists noted the potential for increased drug development costs and longer approval timelines and increased regulation of DTC advertisements. Panellists also discussed the scientific issues underlying the Act’s goal of using administrative databases to identify safety signals, pointing out that such databases can be biased and that there is no consensus among researchers over how to appropriately identify and investigate a safety signal using such data.

Some patient advocacy groups are dissatisfied with the Act. The National Patient Advocate Foundation, for instance, pointed out that patients with life-threatening and life-altering diseases such as cancer draw hope from the process of scientific discovery and new product development. “We support reform that makes drugs safer for their intended populations, but caution against those actions whose unintended consequences might hinder the improvement of technologies for

treatment, prevention, screening and detection – or that discourage their creation altogether.” The legislation does not allow for the sale of some potentially life-saving drugs while they are still in the research phase, another frequent request from patient advocacy groups.

future trends

Given the broad scope of the FDAAA changes, it is difficult to predict all of its long-term consequences. For industry, the likely result will be increased investment in epidemiology, outcomes research and post-approval observational studies over the next few years. Companies will also likely need to begin discussions with the FDA earlier to appropriately plan for any additional study requirements or post-approval commitments. The academic community may find expanded funding opportunities for research into methods of analysing and interpreting observational data, both from prospective post-approval studies and from administrative databases. In particular, the FDA is planning to invest in this area to develop and test new methods for signal detection, data mining and analysis of claims or electronic health record data. The agency plans to develop guidelines on pharmacoepidemiological studies to support this research. The guidelines may help to increase the usefulness and value of data from these types of studies.

The number of post-approval research studies will most likely increase significantly as companies work to meet the new FDA requirements or attempt to proactively manage safety concerns. As the number of ongoing studies rises, researchers may find it increasingly difficult to recruit participants for their studies. For example, healthcare providers may become overwhelmed with post-approval studies and REMS requirements and be unwilling to participate in additional research. This will make other data sources more important for safety monitoring; in particular, data standards that allow for the integration of data from electronic health records and other databases into

observational studies will be critical for the long-term success of this approach to managing safety.

As these types of observational research become more common, in particular those that require patient participation in a study to receive medication (eg, some REMS programmes), the boundaries between care and research may become blurred, raising potential problems. Current privacy and research regulations are incomplete relative to these issues and additional guidance from such groups as the Office for Civil Rights (charged with enforcing HIPAA (Health Insurance Portability and Accountability Act of 1996)) or the Office for Human Research Protections (which oversees implementation of the Common Rule) or new legislation may ultimately be needed. Other issues include questions over who is responsible for generating and reviewing the data for these studies, how the data are managed and publicised, and who owns the data.

The FDAAA represents a sweeping overhaul of the US system for ensuring the safety of approved drugs. The legislation includes over 200 provisions dealing with nearly all aspects of the FDA’s work and requires substantial changes in the agency’s approach to drug safety. Strong leadership from within the FDA will be necessary to implement these changes without alienating stakeholder groups, and all these efforts will require continued Congressional support through funding.

Change of this scope in a complex federal agency will not be easy; the full implications of the FDAAA and the agency’s increased emphasis on post-approval safety will likely not be understood for several years.

Dr Richard Gliklich is president and Michelle Bertagna Leavy is a research associate at Outcome Sciences, Outcome Europe Sarl (d/b/a Outcome).

F-D-triple-A steps out to a mixed reception

The FDAAA includes over 200 provisions dealing with nearly all aspects of the FDA’s work and requires substantial changes in its approach to drug safety. The agency will need to move forward carefully to maintain support among multiple stakeholder groups, explain Dr Richard Gliklich and Michelle Bertagna Leavy

The passage of the Food and Drug Administration Amendments Act (FDAAA) in September 2007 was a major milestone for drug safety efforts in the US. While the extensive new legislation gives the US FDA more resources, authority and regulatory tools to ensure drug safety, the most important point of the Act may be its mandate that the FDA shift its safety paradigm.

The Act directs the FDA to develop a systematic, scientifically sound approach to managing the risk/benefit ratio of a drug throughout its lifecycle, with an explicit focus on post-approval safety. Rather than passively waiting for data on potential safety issues, the FDA must now develop methods of seeking information through a proactive surveillance system and increased requests for, and reviews of, post-marketing trials. The implementation of the FDAAA will likely result in challenges for clinical researchers who will need to design and interpret new safety studies, drug manufacturers that sponsor such studies, and regulatory officials who must use these new data to support decision-making. Given the wide impact of the legislation, the FDA will need to move forward carefully to maintain support among multiple stakeholder groups.

Several key changes included in the FDAAA were first raised as part of a 2006 Institute of Medicine (IOM) report entitled, *The Future of Drug Safety*. The FDA commissioned this report in the wake of Merck & Co’s withdrawal of its COX-2 inhibitor Vioxx (rofecoxib) in 2004 to provide recommendations on improving drug safety. The report concluded that the drug safety system needed major changes and went on to provide 25 detailed suggestions as to how to address labelling issues, clarify the FDA’s authority, require registration of clinical trials and results, and improve the science of drug safety. The report also recommended that advertising for new drugs be restricted and that patients be informed of the potential

This March, the FDA began implementing new post-approval monitoring procedures as part of the Safety First/Safe Use initiative

risks of newly approved medicines. While the FDA could implement some of these suggestions immediately, many of the recommendations required Congressional action.

The Congressional response to the

IOM report was swift and sweeping, driven largely by a broad public perception that the FDA was failing in its mission to ensure drug safety. In 2004, just months before the withdrawal of Vioxx, selective serotonin reuptake inhibitors (SSRIs), a widely used type of antidepressant medication, were linked to higher suicide rates. In 2005, the manufacturers of Tysabri (natalizumab), Biogen Idec and Elan, voluntarily recalled the multiple sclerosis drug after three clinical trial patients developed progressive multifocal leukoencephalopathy (PML), a serious viral infection of the brain. The drug was later re-introduced with a mandatory risk minimisation programme. Another safety issue emerged in 2007 when one research group’s meta analysis suggested that GlaxoSmithKline’s Avandia (rosiglitazone), a drug used to treat type 2 diabetes, potentially increased the risk of heart attacks and heart-related deaths in patients using the product. While there is some debate over the validity of the science behind these drug safety issues, the events nevertheless attracted widespread media coverage and criticism of the FDA, creating a political climate in which there was strong support for the major changes proposed in the FDAAA.

provisions of the FDAAA

The FDAAA attempts to address many of the drug safety issues raised in the IOM report. First, the Act gives the FDA increased authority to mandate and monitor post-approval safety studies. The purpose of this change is to enable the agency to proactively monitor new drugs for safety signals and require labelling changes or other risk minimisation activities as necessary. The FDA now has the authority to require post-approval observational studies or clinical trials to monitor a known serious risk, gather more information on signals of a serious risk, or further research an unexpected serious risk. While the FDA has been able to request such studies for some time, its ability to pressure sponsors to conduct the studies was limited. A 2006 FDA report found that sponsors had failed to even start 65% of the approximately 1,200 requested studies. However, under the new legislation, the FDA can levy civil monetary penalties for non-compliance with post-approval study requirements; these penalties can be as high as \$10 million for a single ongoing violation.

This March, the FDA began implementing new post-approval monitoring procedures as part of the Safety First/Safe Use initiative. This programme is attempting to apply clear objectives, standards and timelines, such as those used in the pre-approval process, to the post-approval world. The project will primarily focus on internal FDA processes and policies, with the objective of developing and maintaining interdisciplinary teams to review the safety of approved drugs.

In addition to expanding the role of post-approval studies and surveillance, the FDAAA also increases the ability of the FDA to require risk evaluation and mitigation strategies (REMS), both as part of the drug approval process and once a product is on the market. REMS are comprehensive programmes aimed at ensuring that a drug's benefits outweigh its risks. These programmes are not new; the FDA has been using some

Table 1: Selected US risk management programmes

Product	Manufacturer	Indication	Adverse effect	Risk management programme
Clozaril (clozapine)	Novartis	schizophrenia	agranulocytosis	patients must provide a white blood cell count and an absolute neutrophil count before the drug can be dispensed initially and for refills
Thalomid (thalidomide)	Celgene	multiple myeloma	teratogenic effects	patients must have frequent pregnancy tests; physicians, pharmacists and patients must be part of a registry and regularly attest that they understand the risks and rules
Trovan (trovafloxacin)	Pfizer	infection	serious liver injury	patients must receive the drug at an in-patient facility
OxyContin (oxycodone)	Purdue Pharma	moderate-to-severe pain	abuse/addiction	restrictions on physician prescribing, pharmacy distribution and patient access

Source: GCPJ, Health Affairs

form of risk minimisation programmes (formerly called RiskMAPs) for over 20 years. In general, risk management activities include some combination of three elements: patient and physician education programmes and materials to raise awareness of the specific risks; reminder systems that require certain steps to be taken before a prescription can be dispensed (eg, stickers must be affixed to the patient's chart and the prescription); and distribution and use restrictions to prevent unsafe use.

The first of these programmes was launched in 1988 to manage the risks of Roche's acne therapy Accutane/Roaccutane (isotretinoin). Other large risk management programmes are in place for Novartis's antipsychotic Clozaril (clozapine) and Celgene's multiple myeloma treatment, Thalomid (thalidomide), among others (see Table 1). The FDA initially published guidance on risk management plans in 1999, and has used risk management plans focusing on five types of serious drug side-effects: birth defects, anaphylaxis, abuse/addiction, sudden cardiac or CNS death, and organ destruction.

While the FDA has typically required a risk management programme as part of the drug approval process, the new legislation provides the agency with increased authority to require REMS at any point in a drug's lifecycle based on new safety information. The new data can come from clinical trials, adverse

event reports, post-approval studies, and peer-reviewed biomedical literature (including reviews of existing data). According to the statute, the FDA may determine that a REMS is necessary based on the following factors:

- The estimated size of the population likely to use the drug involved;
- The seriousness of the disease or condition that is to be treated with the drug;
- The expected benefit of the drug with respect to such disease or condition;
- The expected or actual duration of treatment with the drug;
- The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug; and
- Whether the drug is a new molecular entity.

The FDA can assess REMS at specified points to examine their effectiveness. In addition to these individual assessments, the legislation requires evaluation of the concept of a REMS as a risk management tool. The Act also requires that REMS be compatible with established systems for dispensing drugs and not be unduly burdensome to patients. In March 2008, the agency identified 16 approved products that must have a REMS in place under the new regulations; manufacturers of these

products have until this September to submit their proposed strategy. The FDA is also planning to issue additional guidance to industry to clarify the expectations and objectives of REMS.

Both REMS and post-approval studies focus on gathering new data. To ensure that all existing drug safety data are made public, the Act requires that biopharmaceutical manufacturers publicly post the results of all clinical trials involving approved drugs. The FDA can then use these data, along with data generated from post-approval studies and REMS, to demand labelling changes to approved products. The FDA can also require labelling changes or other actions based on data that it gathers through its own surveillance system. MedWatch, the FDA's current adverse event monitoring programme, is a passive system under which the agency relies on patients and physicians to report adverse events. Under the new legislation, the FDA must set up an active risk identification network. This will comprise a master database with data from several sources, such as the Department of Veterans Affairs, the Centers for Medicare & Medicaid Services (CMS), and other administrative databases. The FDA will actively monitor the database for new safety signals related to approved products.

In addition to these new safety initiatives, the Act reauthorises the Prescription Drug User Fee Act (PDUFA) and enables the FDA to use PDUFA funds to improve the drug safety system. The FDA plans to use these resources to focus on addressing the complete lifespan of biopharmaceutical products by adopting new scientific approaches, improving communication between pre-approval and post-approval groups, improving tools for adverse event detection, and commissioning external research on improving drug safety.

In support of these goals, the FDA has begun the process of developing guidance on pharmacoepidemiological studies and held a public meeting this

May. The FDA will also institute post-approval reviews for all new products; the reviews will be conducted at either 18 months after approval or when 10,000 patients have been exposed to the product (whichever event is later). Lastly, the Act establishes the Reagan-Udall Foundation, a private, independent non-profit organisation made up of experts with diverse backgrounds. Its mission is to modernise the FDA and complete scientific work to support the agency's objectives.

implications of the FDAAA

An immediate result of the Act is a large hiring effort at the FDA. The many new initiatives outlined in the legislation will require large numbers of scientific and administrative personnel to implement

An immediate result of the Act is a large hiring effort at the FDA

and manage them, and the FDA is aggressively recruiting new employees, with a goal of adding 1,300 new staff members by October.

From the industry's standpoint, the new legislation will most likely result in an increased resource commitment to drug safety, regulatory, risk management and epidemiology departments. New drug approvals may take more time, and advertising and labelling for new products may be more restricted. In addition, drug approvals may come with strings attached, in the form of post-approval study or REMS requirements. Manufacturers will also need to respond promptly to emerging safety signals for approved products; under the Act, the FDA can require that a manufacturer submit a REMS for an approved product within 120 days. Overall, the Act will likely make drug lifecycle management more complex, more costly, and resource-intensive for manufacturers.

From a healthcare provider and patient standpoint, the Act may make it more difficult to prescribe and use drugs that are covered under REMS. These

programmes could require patients to undergo certain tests (eg, for pregnancy or white blood cell counts) before obtaining a prescription, or mandate that physicians complete training programmes before prescribing some drugs. This could limit patients' access to some medications. For example, programmes that require a physician to be certified may in effect limit prescribing power to highly-trained specialists. Rural or poor patients may not have access to these specialists and may therefore be unable to obtain the medications. Patients may also feel the effect of a more costly drug development cycle in the form of higher prescription drug prices. Health providers may also view the plans as taking decision-making power away from practitioners and patients and putting it into the hands of the government.

And from a research standpoint, scientists may have more employment opportunities as industry and the FDA hire more staff to design, implement and analyse REMS and post-approval studies, but they may also face challenges in recruiting for studies, as physicians become involved in more post-approval research projects.

stakeholder response

Stakeholders' responses to the Act have been mixed. Congressional leaders have championed the legislation as a far-reaching solution to the agency's inherent problems. After the bill's passage, Senator Charles Grassley was quoted in the *New York Times* as saying: "Problems are systemic, and solutions must reflect a new mindset by the agency leadership." As chair of the Senate Finance Committee, Senator Grassley supervised the Senate's drug safety investigations. Doctors Bruce Psaty and David Korn, members of the IOM Committee on the Assessment of the US Drug Safety System also welcomed the legislation as addressing many of the suggestions of the 2006 IOM report.

In a commentary published in *JAMA* in 2007, they stated: "Congress has