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Changes in FDA's Approach to Risk

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An update on the Agency's 2007 Act to improve drug safety sheds more light on REMS regulations.
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Drug safety efforts in the United States underwent a fundamental change in September 2007 with the passage of the Food and Drug Administration Amendments Act (FDAAA). 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 postapproval safety.

The legislation, with over 200 provisions affecting most areas of the FDA, gives the agency more authority to require postmarket epidemiology studies and trials; requires sponsors to make safety related labeling changes; and requires sponsors to develop and comply with risk evaluation and mitigation strategies (REMS). Title IX of the Act took effect 180 days after enactment in March 2008. The new law creates a significantly new vision for drug safety and postmarketing vigilance in the United States, and its implementation will be challenging.

Background

Public attention has focused on drug safety in recent years, largely due to several high-profile products receiving media attention, including:

- Merck's Vioxx, a prescription painkiller that was pulled from the market in 2004 due to potential cardiovascular risks
- Selective serotonin reuptake inhibitors (SSRIs), a widely used type of antidepressant medication that was linked to higher suicide rates¹
- Tysabri, a multiple sclerosis drug voluntarily withdrawn after three clinical trial subjects developed progressive multifocal leukoencephalopathy (PML), a serious viral infection of the brain² (Tysabri was later reintroduced with a mandatory risk minimization program).³

While there is some debate on the validity of the science behind these drug safety issues, the events attracted widespread media coverage and criticism of the FDA, creating a political climate in

which there was strong support for major changes in the US drug safety system.

In 2006, the Institute of Medicine's (IOM) report "The Future of Drug Safety," added significant weight to the call for changes to the drug safety system.⁴ The report, commissioned by the FDA in the wake of the Vioxx withdrawal, concluded that the drug safety system needed major changes and provided 25 detailed suggestions for how to address labeling 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 risks of newly approved medicines. The FDAAA passed just a year later and includes several of the key changes proposed in the IOM report.^{5,6}

FDAAA

While the Act includes numerous changes to the agency, most of the legislation dealing with drug safety is in Title IX. Below is a summary of the key changes related to drug safety introduced in the law.

Increased authority to monitor drugs after approval. The FDAAA gives the FDA authority to require studies at the time of approval or after approval based on new safety information. The agency can also require labeling changes or other risk minimization activities, if necessary. The ability to require new studies must be based on scientific data and is limited to certain specific purposes including:

- Assessing a known serious risk related to the use of the drug
- Assessing signals of serious risk related to use of the drug
- Identifying an unexpected serious risk when available data indicates the potential for a serious risk.

The ability to require a study is further limited by the need to find that the adverse event reporting and the active postmarket risk identification and analysis system—which are to be established under the Act—will not be sufficient to meet the purposes without the study. While the FDA has been able to request these actions for some time, their

ability to enforce the requests was limited, and significant public concern arose over a 2006 FDA report that concluded that sponsors had failed to start 65% of the approximately 1200 requested studies.⁷

Under the new legislation, the sponsor must submit a timetable for completion of the study or trial, provide periodic reports on the status of the required study (including whether enrollment has begun), the number of participants enrolled, the expected completion date, and any difficulties encountered in completion. The study must also be registered on www.clinicaltrials.gov. The FDA can levy civil monetary penalties for noncompliance with postapproval study requirements. These penalties can be as high as \$10 million for a single ongoing violation.

New requirements for risk management. The FDAAA enables the agency to require REMS, both as part of the drug approval process and once the drug is on the market. REMS are comprehensive risk management programs aimed at ensuring that a drug's benefits outweigh its risks.

Safety-related labeling changes. The Act gives the FDA new authority to require labeling changes based on new safety information. The FDA must promptly notify the sponsor if it becomes aware of new safety information that should be included in the labeling of the drug. After notification, within 30 days the sponsor must submit a supple-

ment proposing changes or notify the FDA that they do not believe a labeling change is warranted and state why not.

Increased transparency. The Act aims to improve transparency and communication about risks by requiring manufacturers to post the results of all clinical trials involving approved drugs. The FDA can then use the data, along with data generated from postapproval studies and risk management programs, to demand labeling changes to approved products. The FDA can also require labeling changes or other actions based on data that it gathers through its own surveillance system.

FDA can levy civil monetary penalties for noncompliance with post approval study requirements as high as \$10 million.

In addition, the FDA must now maintain a consumer-friendly Web site that contains summaries of drug safety information. Once a drug has been on the market for 18 months or used by 10,000 patients (whichever is later), the FDA must add a summary analysis of adverse drug events and known risks to the Web site.

Active surveillance. To improve the agency's surveillance system, the legislation requires FDA to launch an active risk identification network. This will be comprised of a master database with data from several sources, such as the Department of Veterans Affairs, the Centers for Medicare & Medicaid Services, and other administrative databases. The FDA will actively monitor the database for new safety signals related to approved products. This is in contrast to the current system, MedWatch, in which the FDA relies on patients and physicians to report adverse events and does not conduct proactive surveillance.

The distributed research system, including multiple electronic data sources that will be the cornerstone for building the active surveillance system, has been named Sentinel. For more information about the Sentinel Initiative, go to <http://www.fda.gov/oc/initiatives/advance/reports/report0508.pdf>.

Increased funding and scientific support. In addition to these new safety initiatives, the Act reauthorizes the Prescription Drug User Fee Act (PDUFA) and enables the FDA to use PDUFA funds to improve the drug safety system. The Act also establishes the Reagan-Udall Foundation, a private, independent nonprofit organization made up of experts with diverse experiences, with the purpose of modernizing the FDA and completing scientific work to support the agency's objectives.^{5,8}

Since the passage of the Act, the FDA has begun implementing its new requirements through the Safety First/Safe Use initiative. The guiding purpose is to ensure drug safety throughout the drug lifecycle by giving an equal focus to oversight of drug development and postmarketing safety. Furthermore, the FDA intends to develop multiple (including entirely new) strategies to influence the safe and appropriate use of drugs.

The plan outlined is nothing less than a fundamental change in U.S. drug regulation. It is clear that it is the intent of Congress for the FDA to undergo significant change and that it "must reflect a new mindset by the agency leadership."^{6,9} Safety First/Safe Use 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.¹⁰

Changes in risk management

While the legislation as a whole will have a broad effect on drug safety efforts, the area that has received perhaps the most attention from industry and regulation in recent months has been the REMS. The REMS regulations will change several aspects of risk management programs for approved products. But the concept of using risk management programs (formerly called RiskMAPs) for approved products is not new. The FDA has been using these programs for over 20 years. The first risk management program was launched in 1988 to manage the risks of Roche's acne therapy Accutane/Roaccutane (isotretinoin).¹¹ Other large risk management programs are in place for Novartis's antipsychotic Clozaril (clozapine) and Celgene's multiple myeloma treatment Thalomid (thalidomide), among others. Table 1 includes some examples of risk management programs in the United States.

Risk management is a process encompassing the assessment of risks and benefits with the minimization of risks and the maximization of benefits. A RiskMAP is a strategic safety program designed to meet

specific goals and objectives in minimizing risks. The tool box for RiskMAPs includes product labeling, education and outreach, reminder/prompting systems, and Performance-Linked Access Systems (PLAS). The agency outlined their initial approach to risk management programs in a guidance document published in 1999.¹⁴

In general, the agency has used risk management plans to manage five types of serious drug side effects, as outlined in Table 2. The basic concept of a risk management program and the types of serious risks that it can be used to manage will not change significantly under the REMS legislation. REMS will generally include some combination of the "Elements to Assure Safe Use," which are:

- Health care providers who prescribe the drug have particular training or experience or special certifications.
- Pharmacies, practitioners or health care settings that dispense the drug are specially certified.
- The drug may only be dispensed in certain settings.
- Patients are subject to monitoring or enrolled in a registry.

The major changes in the legislation involve when the FDA can require an REMS and how the REMS are assessed. Currently, the FDA has typically required a risk management program 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 life cycle

A Watchful Eye on Marketed Medicines

Product	Original Manufacturer	Indication	Goal	Risk Management Program
Clozaril (clozapine)	Novartis	Schizophrenia	Prevent agranulocytosis	Monitor white blood cell counts
Thalomid (thalidomide)	Celgene	Multiple myeloma	Prevent fetal exposure	Pregnancy prevention and monitoring for pregnancy
Trovan (trovafloxacin)	Pfizer	Infections	Prevent serious liver injury	Patients must receive the drug at an in-patient facility
OxyContin (oxycodone)	Purdue Pharma	Moderate to severe pain	Prevent abuse/addiction	Restrictions on physician prescribing, pharmacy distribution, and patient access

Source: Outcome Sciences.

Table 1. Examples of Risk management programs in the United States.^{12,13}

On the Lookout: Monitoring Side Effects

Side Effect	Description	Example
Birth defects	Use during pregnancy can produce fetal malformation	Thalomid (thalidomide) Accutane (isotretinoin)
Anaphylaxis	Can result in immediate life-threatening reaction	Ziagen (abacavir) Plenaxis (abarelix)
Abuse/addiction	Overdose can be fatal; drug may be diverted for illegal use	OxyContin (oxycodone)
Sudden cardiac or CNS death	Can cause serious heart-rhythm or CNS problems	Tikosyn (dofetilide) Lindane (gamma-hexachlorocyclohexane)
Organ destruction	Can cause irreversible, life-threatening organ damage	Clozaril (clozapine)

Source: Outcome Sciences.

Table 2. Five types of serious drug side effects monitored in risk management plans.¹³

based on new safety information. The new data can come from clinical trials, adverse event reports, postapproval 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
- 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
- Whether the drug is a new molecular entity.⁵

If the FDA determines that a REMS is necessary, the sponsor must submit a plan for the REMS within 120 days or within another reasonable time frame determined by the FDA. Regular assessments of the effectiveness of the REMS are also required by the legislation. These assessments should take place at 18 months, three years, and seven years after the REMS is approved, but the FDA can stop the assessments after three years if the REMS is adequately managing risks. 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. Manufactur-

ers of these products have until September 2008 to submit their proposed strat-

The new legislation provides the agency with increased authority to require REMS.

egy.¹⁵ The FDA is also planning to issue additional guidance to the industry to clarify the expectations and objectives of REMS.

Implications for sponsors

From an industry standpoint, the Act will likely make drug lifecycle management more complex, more costly, and resource intensive. Manufacturers will likely need to devote more resources to their drug safety, regulatory, risk management, and epidemiology departments. New drug approvals may take more time, advertising and labeling for new products may be more restricted, and some new products may require additional postapproval studies or REMS. For the FDA, full implementation of the Act requires significant expansion of personnel as well as financial resources, only some of which have been promised in the initial legislation.

Conclusion

FDAAA and the roadmap outlined through the Safety First/Safe Use initiative represent a paradigm shift at the FDA toward balancing oversight of drug development with monitoring drug safety postapproval. REMS are just one of a series of significant changes that can have a significant impact on any new drug or any existing drug for which new safety

information is learned. Together, these changes are in fact quite sweeping but will be gated by the need for new staffing and planning at the FDA. Change of this scope in a complex federal agency will not be easy, and the full implications of the FDAAA and the agency's increased emphasis on postapproval safety will likely not be understood for several years.

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