New law gives FDA more influence to monitor drug safety

When the US Food and Drug Administration (FDA) announced on 16 October that the diabetes drug Byetta may cause pancreatitis, a serious and sometimes fatal side effect, most scientists could have been forgiven for being taken by surprise.

There's not a whiff of pancreatitis in the detailed results from the 19 clinical trials of Byetta in two publicly available databases—one launched and maintained by the drug industry and another by Eli Lilly, which, together with Amylin Pharmaceuticals, markets Byetta.

Serious side effects sometimes don't become apparent until drugs are used by large numbers of people after their approval. But companies have also had the choice not to make public the results from trials in which pancreatitis turned up as a serious side effect—until now.

On 27 September, President Bush signed a 422-page law that overhauls the way the FDA monitors drug safety. Among the law's many provisions is the requirement that drug makers begin posting all their clinical trial results for marketed drugs in a database maintained by the US National Institutes of Health.

"In my opinion, this is the single most important provision of this new law," says Steve Nissen, a cardiologist at the Cleveland Clinic who used publicly available results from 42 clinical trials on the diabetes drug Avandia to find that that drug increases the risk of heart attacks (*N. Engl. J. Med.* **356**, 2457–2471; 2007). Those results were only available because New York attorney general Eliot Spitzer had compelled Avandia's maker GlaxoSmithKline to make all of its trial results public as a condition of a 2004 legal settlement concerning the marketing of its antidepressant Paxil.

"For the first time we will have access to the totality of the clinical trial information on marketed drugs," Nissen says. "This will enable the scientific community to appropriately balance benefits and risks."

The new law also requires companies to pay the FDA at least $434 million each year for the next five years to support the speedy review of their products. An additional $225 million in new user fees will be directed toward monitoring the safety of approved drugs. Over the next five years, the agency will also assemble a database containing the electronic medical records of 100 million patients, which experts will be able to mine to detect emerging problems with drug safety before they become public health disasters.

The law also gives the $1.9 billion agency substantial new powers to police the safety of marketed drugs. Among other things, the agency will be able to enforce label changes on marketed drugs, rather than negotiate them with drug makers as it now does, and require companies to conduct additional studies on drugs—from observational reports to full-fledged clinical trials—when safety concerns emerge. Companies that flout requirements could face up to $10 million in civil penalties.

"This is a good deal for patients," says Randall Lutter, the FDA's deputy commissioner for policy. "It gives us money and, through that, the ability to hire the needed expertise. And it gives us authorities we think we can use well to help patients."

Representatives of the industry are somewhat less enthusiastic. "A lot is going to have to be looked at very carefully with regard to these enhanced post-market safety authorities," says Alan Goldhammer, deputy vice president for regulatory affairs at the Washington, DC-based Pharmaceutical Research and Manufacturers of America. How the FDA deploys its new powers "is a bit of a black box at this point in time," he says.

The industry would also have preferred to fund less than the 60% of drug review costs the new law mandates, Goldhammer adds. "We would be more comfortable if this was 50% from user fees and 50% from [the government]."

The law is, in part, Congress's answer to a rash of safety issues that have plagued the agency in recent years, including the 2004 recall of Merck's painkiller Vioxx and the controversy this spring over Avandia. Last year, the Institute of Medicine issued a scathing set of recommendations meant to improve the FDA's functioning. And on 28 September, the day after the new law came into effect, a report from the inspector general of the US Department of Health and Human Services said that the agency's inspections of clinical trials are plagued by incomplete data, lack of coordination and poor follow-up.

For academics who aren't privy to companies' privileged data, the new clinical trials registry promises to be the most significant change made by the new law, as it could allow for more analyses like Nissen's report on Avandia. "The results registry is potentially far more information than has previously been developed," says Bruce Burlington, a former FDA official who was vice president of Wyeth until August.

There are some details of the new law that have yet to be worked out. For example, it is not yet clear whether the trial registry will include results from trials on drugs that aren't approved by the FDA. "That's one of the pieces of this legislation that we will be watching closely," Burlington says. "Does this turn into something really useful or does it not live up to its promise?"

Some critics say that, even with the considerable changes it makes, the new law fails to make the single leap that could avert another Vioxx-like disaster. "This law does nothing to change the way FDA makes decisions," says David Graham, the FDA safety officer whose warnings about Vioxx went unheeded at the agency.

"The people who approve a drug in the first place are still the ones who make decisions about whether it stays on the market and how it is regulated. The legislation doesn't address that," says Graham. "I predict that we will continue to have future drug-safety disasters because of this."

Meredith Wadman, Washington, DC

More power to the FDA: A new law gives the agency more authority to monitor drug safety.

According to the new law, the FDA can:

- force drug makers to change labels on marketed drugs
- demand clinical trials on marketed drugs
- fine companies up to $10 million for noncompliance
- expect at least $2.1 billion from industry over five years to speed drug reviews
- collect $31.25 million from companies over five years for the review of television ads
- establish a database containing the electronic medical records of 100 million people