

# SAFETY SYSTEM

As recent studies conclude that some already-to-market drugs may be linked to serious illness, it has never been more important for pharma to be fully protected.

**John K Jenkins** and **Joseph C Famulare**, US FDA, discuss the steps manufacturers should take to ensure adequate cover.



In November 2007, Merck & Co, makers of Vioxx, agreed to pay \$4.85 billion compensation to settle claims that the drug had caused strokes and heart failure. The Vioxx case provoked debate over drug safety in the US and in particular the US FDA's role in monitoring product safety.

Statistically, however, the number of drugs that are withdrawn from the US market has shown little change over several decades.

'We occasionally see a blip upward but as far as averages over a longer time course, about 2.5% to 3% of drugs that are approved are eventually withdrawn for safety reasons and that seems to be fairly stable,' says John K Jenkins, MD, director of office of new drugs, Centre for Drug Evaluation and Research (CDER), FDA.

Something he has noticed is that the reasons for withdrawal have shifted away from past issues of drug-induced liver toxicity or arrhythmias. 'We've seen drugs that have shown over long-term studies to increase the rate of common events that are part of the patient's medical background,' he adds.

One example was Vioxx. This was not withdrawn because it caused liver toxicity, but because it increased the rate of heart attack, very common in the background of the population

## Author profiles



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## KEY POINTS

- Withdrawal reasons are moving away from liver toxicity.
- The US government believes fee increases will help the FDA become more effective in enforcing public safety.

taking that drug. It is very difficult – if not impossible – to pick up from spontaneous adverse reporting systems.

'Trials are needed to pick up those types of changes,' Jenkins adds. 'That shift has been of interest to us: the actual reason for the withdrawal.'

During the 1990s, the FDA introduced a user fee programme for drugs seeking approval. The programme was designed to offset the regulatory cost of researching and bringing a drug to market. A comparison of withdrawal rates pre- and post-user fee programme has shown little change (Figure 1). However, the user fee programme has had a more significant effect on the efficiency of the FDA in the drug approval process. The increase in speed has been mistaken for a 'rush to market mentality' within the FDA process and is often labelled by critics as the cause of recent increases in medication withdrawals.

'It's important to understand that the user fee gave us additional resources,

so we could complete our reviews in a more timely manner, but it didn't change the standards for approval,' says Jenkins. 'So any improvement to the "time to approval" is really a function of increased resources to get the reviews done and process efficiencies we've instituted in our review process. The actual data requirements and the risk/benefit analysis haven't changed since we've had user fee.'

## FDAAA and fees

The FDA has been focused on defining and implementing the FDA Amendment Act of 2007 (FDAAA). This 400-

Figure 1. US drug withdrawal rates

Year of approval	Number withdrawn	Number approved	Percentage withdrawn
1979-83	3	95	3.2%
1984-88	5	113	4.4%
1989-93	3	127	2.4%
1994-98	4	172	2.3%
1999-2000	1	60	1.7%

page law will require time and careful consideration before being assimilated into its processes. Included was a revised Prescription Drug User Fee Act (PDUFA IV), which has received a mixed reception.

Critics of PDUFA IV say the fees have been designed to substitute federal appropriations, thereby placing financial responsibility directly on the pharmaceutical industry and making the FDA a predominantly 'industry funded' body. However, the US government believes fee increases will help the FDA become more effective in enforcing public safety standards and monitoring clinical trial data in an industry where research is frequently conducted internationally.

The increased fees will help to expand drug safety monitoring programmes both within the US and abroad, allowing the FDA to monitor the full lifecycle of a drug from pre-approval to longer-term post-market release. The funding will also enable the FDA to increase staff numbers to support the additional monitoring programmes and update their drug tracking technology.

### Multiregional clinical trial data

Monitoring remote research facilities poses its own unique challenges. The FDA is a signatory to the International Conference on Harmonisation, a project that aims to harmonise the interpretation of technical and clinical requirements for drug registration with a view to reducing the need for duplication in testing between countries and enabling faster approval times with minimal resource waste.

'When considering multiregional studies and data, we are always concerned about the issues we normally consider with clinical trials and particularly when they are coming from areas of the world that we are not familiar with, and that have different standards of medical practice, ethical standards and regulatory standards,' explains Jenkins. 'So, we have to look at the clinical research outsourcing to different parts of the world very carefully as we analyse the data to decide if the findings of the studies are applicable to the US population.'

Recent years have revealed that clinical trials conducted abroad, in regions with more homogenous populations, have shown efficacy rates that cannot be duplicated within US clinical trials. 'So, the differing results are a puzzle that we have to work through and try to understand,' says Jenkins.

From the Office of Compliance standpoint, ensuring the accuracy of multiregional data and clinical trials brings logistical challenges. 'We work closely with the office of new drugs reviews divisions, to determine which research sites are appropriate for conducting clinical trials, be they domestic or foreign,' says Joseph C Famulare, deputy director, office of compliance, CDER, FDA. 'And we inspect foreign sites we choose using the same standards we expect

in the US. These are in our inspection programme, available online in our compliance regulations.'

Clinical investigators hired abroad serve as FDA monitors and are thoroughly briefed on US ethical standards and human subject protection guidelines in order to properly assess facilities.

'We also expect the sponsor and/or a contract research organisation brought in by the sponsor to properly monitor these sites to ensure that the clinical trial data is accurate and our standards of human subject protection are met in terms of safety in conducting these trials,' says Famulare.

### Approvals approach

There has been speculation that the FDA has quietly modified its approach to drug approvals and that new drugs are subject to a comparative effectiveness standard, whereby the drug is compared to existing drugs, within its class, currently on the market. The suggestion is that, if the new drug cannot demonstrate significant benefits beyond drugs that are already available, the application would be rejected. But Jenkins assures this is not the case and that every application is looked at on its own merit.

'We have to make sure we have enough data and that it comes from high quality trials.'

'We don't have any particular goal of how many we approve in a given year,' says Jenkins. 'Every decision is based on a risk/benefit analysis. It's easier to be first in a class than it is to be later in the class because as we gain more experience, we learn more about the drug's safety concerns. It would be irresponsible for us as a public health agency not to apply those new insights to our decision-making process. And if the product has a serious safety concern that has not been identified in other available products, we naturally look to see if the product offers any benefit.'

In terms of how pharma can help to ensure drug safety, Jenkins advises they need to make sure that the data available to the FDA before approval is adequate.

'There's a lot of uncertainty at the time that a drug is approved and we as a society accept some of that uncertainty in trade off to having access to the drugs earlier,' he says.

But there are trade-offs that society has to make on how much risk would be acceptable when something unexpected occurs after approval versus the value of getting the drug available to patients sooner. 'We have to make sure we have enough information when it comes to approval and that the data comes from high quality trials, which are adequately monitored and follow all of the appropriate procedures before approval,' says Jenkins. **WPF**