

## New Risks, New Plan

Drug safety concerns show need for sophisticated risk management.

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**A**rocoxia, Vioxx, Acomplia, Zelnorm, and Tysabri; Aranesp, Procrit, Avandia and Lucentis. The concerns raised about these drugs illustrate the unprecedented focus on both safety and costs not only at the Food and Drug Administration but also in Congress and at the Centers for Medicare and Medicaid Services.

From the FDA's enhanced concerns about safety to Congress' consideration of bills authorizing the FDA to impose ongoing risk management programs and post-market studies, as well as the CMS' increasing interest in requiring pharmaceutical companies to demonstrate cost and comparative effectiveness, the landscape of drug and biologic development is rapidly and irrevocably changing. These changes will have dramatic consequences for the process of selecting drug candidates, the scope and type of clinical studies, and the market value of products and companies. Pharmaceutical companies must respond by better integrating their own risk management strategies.

### THE FDA'S NEW FOCUS

The market has seen the highly publicized withdrawals of several widely used drugs—including Merck's Vioxx and Pfizer's Bextra—because of significant safety issues that arose after FDA approval. Not surprisingly, this has had ripple effects at the FDA itself. In a host of ways, the agency has been increasing its oversight of new and already-approved drugs.

For example, there has been a substantial increase in health advisories. In 2001, the FDA issued four. By 2005 and 2006, the number had risen to 16 a year.

Greater evidence of comparative safety or efficacy may be required for approval of new drugs where other therapeutic products are on the market. The FDA's "not approvable" decision on Merck's arthritis drug Arcoxia, for example, has been widely seen as indicating a more conservative approach.

That same conservatism appears to have affected the agency's weighing of the risks and benefits of Sanofi-Aventis' diet drug Acomplia. After issuing an initial "approvable" letter, the agency reversed its determination that an "obesity management" indication for Acomplia could be approved without an advisory committee

review meeting. Last week that committee unanimously rejected Acomplia on safety grounds.

At the same time, the FDA is sharpening its oversight of approved drugs, illustrated by Novartis' recent suspension of sales for Zelnorm at the FDA's request. An outside reviewer's *post hoc* analysis of clinical trials revealed an increased risk of cardiovascular events for Zelnorm users. But that analysis showed that only 13 patients (0.1 percent) had serious events, out of 11,614 patients in 29 studies.

The FDA has been evaluating whether additional safety warnings for other products—including the diabetes drugs Avandia from GlaxoSmithKline and Actos from Takeda—are needed to highlight a possible risk of congestive heart failure in certain patients.

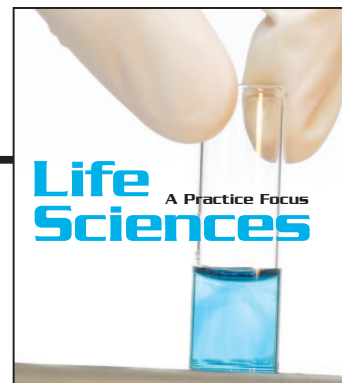
Similarly, the FDA convened its Oncologic Drugs Advisory Committee to reassess the risk-benefit profile of certain anemia drugs, such as Amgen's Aranesp and Johnson & Johnson's Procrit, to address new concerns over their use with cancer patients. The advisory committee unanimously recommended that additional safety studies be conducted. It also voted in favor of added "black box" warnings on the product labels.

Another way in which the FDA has reacted to growing public concern about drug safety is by imposing risk minimization action plans, or RiskMAPs. The agency in 2005 issued guidance documents on RiskMAPs, which can effectively limit the scope of the distribution and sale of products. For example, the recent RiskMAP adopted for Biogen Idec/Elan's multiple sclerosis drug Tysabri required that the drug makers create a mandatory patient registry, mandate a preliminary MRI, and make the drug available only through authorized doctors or centers.

In addition, the agency has increasingly obliged drug developers to agree to undertake post-market clinical studies, generally referred to as Phase IV studies. (The efficacy of this requirement, including the effectiveness of the FDA's oversight, has been widely questioned.)

### CONGRESSIONAL EFFORTS

While the FDA has been doing more with its current authority, public outcry over drug safety has stimulated congressional inter-



est as well. Congress has undertaken hearings both on safety issues affecting specific drugs (such as Avandia) and on broad legislation to enhance FDA authority. Proposals have exploded in number. From 1989 to 1998, no bills containing the words “drug safety” were introduced. From 2003 to 2004, there were 19. And from 2005 to 2006, there were 21.

This year the Senate passed the Food and Drug Administration Revitalization Act, which requires a particularized “risk evaluation and mitigation strategy” if serious risks are uncovered during a drug’s clinical trials and post-approval studies or through the FDA’s adverse event reporting system or outside studies. The bill also mandates that the agency create an active post-approval drug surveillance system and provides significant civil penalties—up to \$2 million—for companies that fail to comply with the risk mitigation requirement.

Mark McClellan, the former head of both the FDA and the CMS, has commented that this legislation would constitute “the biggest set of changes in post-market drug regulations since at least 1962,” with the FDA “doing no less than entering a new era of post-market drug regulation.”

McClellan has also observed that more generally, new drug safety laws could be expected to create new interactions between the FDA, the CMS, and private payers as part of the development of cost containment mechanisms under the Medicare prescription drug benefit. Legislation has recently been introduced in the House, for example, to provide additional funding to compare the cost and effectiveness of various treatments for particular illnesses.

### **CMS ACTIVITIES**

Perhaps most surprisingly—in view of its traditional lack of involvement in this area—the CMS has begun to consider a role in drug safety and effectiveness matters. The driving force is the strongly felt need to contain the costs of the Medicare drug benefit.

So far, the CMS has proposed restrictions on coverage and reimbursement for anemia drugs, such as Aranesp and Procrit, in view of the new label warning for certain cancer patients. The CMS is also reviewing its coverage policy for these drugs when they are used to treat kidney disease. Because these drugs are the single largest expenditure for Medicare, limitations on the scope of coverage or reimbursement could result in substantial savings for the government. A Wall Street pharmaceutical industry analyst observed, “We could never have anticipated that the extent of the regulatory and reimbursement threat could reach these levels.”

There is a similar substantial interest in developing mechanisms to research the comparative effectiveness of medical treatments. The Congressional Budget Office is preparing a report on the potential for such research to reduce costs and improve treatment. And Gail Wilensky, the head of the CMS’ predecessor agency, has proposed a new quasi-governmental entity to oversee such research. Private insurer groups have also supported the idea.

This quasi-governmental entity might be modeled after the United Kingdom’s National Institute for Health and Clinical Excellence, which has become active in evaluating clinical effectiveness and cost-effectiveness. The U.K. agency concluded, for example, that Tysabri is not cost-effective for routine treatment of multiple sclerosis.

The first comparative effectiveness trial of a pioneer drug undertaken by the National Institutes of Health was announced in February this year. The trial will compare two Genentech drugs, Lucentis (which costs \$2,000 a dose) and Avastin (which costs \$40 a dose). The potential Medicare savings from use of the less expensive drug are estimated at as much as \$1 billion a year.

### **NEW STRATEGY NEEDED**

This unprecedented confluence of interest among the FDA, Congress, and the CMS on drug safety, comparative effectiveness, and cost issues makes it imperative that pharmaceutical and biotechnology companies develop their own more sophisticated risk management strategies.

The effects of all these government efforts on drug developers are likely to be substantial. They include more restricted distribution, and consequently sales, of some drugs; reductions in coverage and reimbursement by the government and private payers based on new comparative clinical effectiveness and cost-effectiveness studies; and the resulting effects on the market’s valuation of drugs and their manufacturers, which could, in turn, affect negotiations over collaboration agreements, mergers, and acquisitions.

Traditionally, drug developers have narrowly focused their clinical trials on generating sufficient safety and efficacy data to obtain FDA approval as quickly as possible. Pricing and reimbursement issues were rarely addressed before that approval. Indeed, they seldom needed to be addressed at all, because nearly every approved drug was reimbursed at whatever price level the manufacturer set.

That system is no more. In this new era of greater focus on safety and cost, developers of drugs and biologics must make their own risk management plans up front.

For example, clinical trials today should include tests designed to establish comparative safety and efficacy as well as cost-effectiveness. Such evidence must be ready at the time of FDA approval to answer government and private payer challenges.

Drug developers should also be prepared with their own data and communications strategies to respond to the results of government-directed studies of comparative efficacy. The implications of making supporting data more publicly available at an earlier stage in a product’s life cycle must also be addressed.

Companies will also want to prepare plans to respond to questionable calls for the market withdrawal of a product and to address the risk of class actions, which will surely follow.

Proving the clinical safety and efficacy of a pioneer drug is thus only the beginning. Drug companies must also adjust to these new cost and safety demands with their own improved, better-integrated risk management strategies.

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