diatric clinical trials before the drug can be marketed. Also, in 1997, Congress passed the FDA Modernization Act (FDAMA). Among other things, the act offers drug companies a six-month patent extension as an incentive to conduct pediatric trials. For regulatory purposes, pediatric is defined as between the ages of 2 and 18.

Although the pharmaceutical industry initially opposed the FDA rule, the combined carrot-and-stick approach mollified their objections. "As long as the mandatory testing rule is coordinated with the incentives provision of FDAMA, that's appropriate," says Jeff Trehwitt, spokesman for the Pharmaceutical Research and Manufacturers of America (PhRMA).

The carrot grew larger in January this year, when the Best Pharmaceuticals for Children Act (BPCA) authorized up to US \$200 million in government spending for pediatric clinical trials. The money is not appropriated yet, but it should ultimately help test drugs whose patents have expired, making them ineligible for the incentive offered by FDAMA.

"If you look at the combination [of measures], there has been quite an impact," according to Trehwitt. In the past 3 years, at least 29 drugs have been labeled with FDA-approved pediatric dosing information, compared with only 6 in the preceding decade. PhRMA says that companies are currently conducting over 400 pediatric clinical trials in response to FDA requests. However, the incentives offered by FDAMA and the BPCA only affect drugs that are already on the market. In addition, the incentive programs do not cover vaccines, whereas the Pediatric Rule does.

However, in December 2000, three groups sued the FDA, arguing that the Pediatric Rule was unnecessary and would slow drug approval and delay medicines coming to market for the benefit of patients. According to Sam Kazman, general counsel for the Competitive Enterprise Institute, one of the three groups, the rule allowed the FDA to dictate a drug's indications, mark-

ing "a pretty significant change in the drug-approval framework, because up to now it's been the company that decides."

Hoping to dodge the lawsuit, in March this year the FDA proposed suspending the rule and research advocates and pediatricians immediately cried foul.

"When a drug comes to market under the Pediatric Rule, children will be protected from the very first day [the drug is available]," according to pediatrician Richard Gorman, chairman of the American Academy of Pediatrics committee on drugs. He argues that the

groups filing the lawsuit cannot "name one example where an adult drug has been delayed under FDAMA or the Pediatric Rule," and adds that pediatric trials can provide critical data. For example, Neurontin, a painkiller, was found to require 30% higher dosages in children than had been predicted from adult studies, and Propofol, an anesthetic agent, has been found unsafe for long-term sedation of children. In response to the outcry, on 19 April the FDA reversed its decision to suspend the rule.

Several senators have now rallied behind an effort to codify the rule as a law. And seeking to quell further criticism, the Bush administration points out that \$7 million in funding for federally sponsored pediatric clinical trials has been included in the 2002 budget, at an estimated value of \$3–4 million per trial.

Alan Dove, Philadelphia

FDA criticized for dangerous leniency

While free-trade proponents sue the FDA for being too strict (see main story), a controversial paper published in May accuses the agency of being too lenient.

According to researchers at Harvard Medical School and the Washington-based advocacy group, Public Citizen, the agency's drug-approval process commonly allows dangerous compounds to reach patients.

The FDA and the pharmaceutical industry maintain that the analysis is seriously flawed. But according to independent experts, the paper actually highlights the importance of reforms already being undertaken by both the agency and the industry.

By examining drug-labeling information in the Physicians' Desk Reference for drugs approved between 1975 and 2000, Karen Lasser and colleagues at Cambridge Hospital, Massachusetts, determined that a drug had a 20% chance of acquiring a new 'black box' warning—indicating an adverse event—on its label or being withdrawn from the market over the 25-year period (*JAMA* 287, 2215; 2002). The authors also point out that almost 20 million patients in the US took at least 1 of the 5 drugs pulled from the market in 1997 and 1998. The antibiotic grepafloxacin, for example, was withdrawn two years after approval because it caused cardiovascular problems.

In an accompanying editorial in *JAMA*, two FDA officials argue that black box warnings, which are used to communicate many types of important prescribing information, are a poor surrogate indicator of drug toxicity. And PhRMA argues that the authors' claims of the number of patients affected by adverse drug reactions were based on a discredited meta-analysis.

Chris Milne, assistant director of the Center for the Study of Drug Development at Tufts University in Boston, prefers to take the middle ground. He says that the analysis may have masked recent improvements in the safety of newly approved drugs. In particular, the FDA Modernization Act of 1997 has brought about a series of changes that have only recently begun to affect the approval process. The FDA has undergone administrative restructuring, improved its data-tracking systems and established a public website to allow watchdog groups to monitor the drug-approval process.

Estimates suggest that physicians only report about 10% of adverse reactions to the FDA. Legislation now being considered would allow the FDA to use user fees from drug companies to buy access to commercial drug-usage databases, improving its ability to search for adverse reactions.

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