Is the FDA approving drugs too fast?

Probably not—but drug recalls have sparked debate

Debate in the United States about the optimal amount of time required by the Food and Drug Administration for adequate testing of new drugs has raged since 1962, when Congress established formal criteria for proving drug safety and effectiveness. Through much of the past decade the FDA has been accused of delaying drug approvals: now it is accused of acting too hastily in approving drugs that have later had to be withdrawn.

The height of the initial criticism came in 1995, with the election of a Republican majority in Congress that favoured full privatisation of all healthcare matters. The Republican speaker of the House of Representatives, Newt Gingrich, referred to the FDA as "job killers": its excessive reviews, he claimed, delayed the launch of new drugs and thereby forestalled growth for the pharmaceutical industry.[1]

Although the agency disputed that its reviews were excessive, the FDA had already argued that the increase in the number of drugs seeking approval had stretched the agency beyond its means and was indeed delaying approval of new drugs. In 1992 it had worked with Congress to pass a law requiring pharmaceutical and biotechnology companies to pay a fee for each drug submitted. The money is being used to hire as many as 600 more reviewers and to speed the drug review process with performance targets. The very success of this programme, designed specifically to accelerate the review process, has, however, pushed debate over the speed of approvals in the opposite direction in recent months.

Three new prescription drugs have been recalled in the past 12 months: mibefradil for hypertension; dexfenfluramine for morbid obesity; and, last month, bromfenac sodium for pain. The FDA's critics cite these recalls as evidence that pressure from the pharmaceutical industry and other special interest groups has accelerated the drug review process to the point of endangering public health.[2]

Recalls occur in direct proportion to the number of new drugs approved and launched, however, and an increasing number may be statistically inevitable. Indeed, the number of new drug compounds approved each year by the FDA has more than doubled during the 1990s, from an average of 20 products at the beginning of the decade to 40 in the past two years.[3] Many reasons exist, in addition to the user fee programme, for this mushrooming of newly approved drugs. Firstly, drug companies have an abundance of money for research and development since the launch of several highly profitable drug classes since the mid-1980s—in particular, calcium channel blockers, angiotensin converting enzyme inhibitors, the statins, H_2 antagonists, and selective serotonin reuptake inhibitors. Secondly, activists in AIDS and cancer spurred the agency to adopt a fast track approval process for lifesaving new drugs. Finally, these factors coincided with the advent of better drug discovery and development processes, from combinatorial chemistry in the laboratory to recombinant protein manufacturing in the factory. More money plus better science equals more new drugs.

As a result the total number of drugs reviewed and approved by the FDA could not help but increase. With such increase comes a commensurate increase in the number of drugs recalled. For all its actuarial certainty, this classic expression of the law of averages provides little comfort to FDA critics who dwell on the anecdotes of human suffering associated with each product that is recalled.

Incidence rates for the adverse events that prompted each of the recent drug recalls are similarly inevitable, as new drugs with broad indications are administered to heterogeneous populations far larger than any reasonable clinical trial can replicate via sampling. The analgesic bromfenac, for example, resulted in four deaths and eight liver transplants among 2.5 million treated patients. Such an incidence could not have been detected in the product's clinical trial of 2500 patients.[4] Even if a drug company could afford to sponsor trials large enough to detect events this statistically remote, it would be unable to recruit enough eligible patients.

The occurrence of rare, but recall prompting clinical events may be the inevitable result of market progress, making the drug manufacturers victims of their own success. The boost to the industry from the FDA's adoption of user fees is one source of that success. Another is the impact of managed care. One of the hallmarks of managed care has been the liberalised use of pharmaceuticals, based on the theory of disease management, which reasons that earlier diagnosis and more aggressive treatment and compliance monitoring will lower the long term costs associated with chronic disease. As a result, managed care companies, working in concert with the drug companies, actively promote pharmaceutical care.

There is an irony that managed care—designed to lower healthcare costs—actually boosts the drug business; but from it stems another irony. Wider use of more drugs, which provides pharmaceutical companies with record profits, also exposes them to greater risks of jeopardising that business.[5] More people taking more new drugs will result in larger numbers of adverse reactions. This too is a statistical inevitability that will continue into the foreseeable future and one more bittersweet fact of medical progress.

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