Rezulin Proves the System Works

By ACSH Staff — March 29, 2000

Last week's withdrawal of Warner-Lambert's diabetes drug Rezulin has provoked a predictable outcry from "consumer groups" who charge that the Food and Drug Administration's laxity and haste permits unsafe drugs into the marketplace. Actually, Rezulin's withdrawal shows that the FDA works exactly as intended. Just because a drug is withdrawn does not mean it should not have been approved in the first place.

When it was initially approved in 1997, Rezulin was viewed by officials and physicians alike as a blockbuster drug important enough to be approved under the FDA's newly instituted "fast-track" protocol. Some liver abnormalities were apparently detected during Rezulin's pre-marketing testing, but not in sufficient frequency to halt its approval and release.

The disease Rezulin treats, type 2 diabetes (the form most commonly found in adults), is both dangerous and often refractory to usual remedies. Diabetes is the most common cause of blindness and kidney failure in adults, a major risk factor for heart disease and stroke, and is now being diagnosed more commonly in children as well. It affects 15 million Americans. It is estimated that in the short time since Rezulin's introduction, it has been used to treat 1.9 million people. About 750,000 were still on it—until last week.

Rezulin was popular because it was the first in a new class of diabetes treatments, glitazones, which have a unique mode of action, enhancing the body's sensitivity to its own insulin and reducing the amount of sugar produced in the liver. And, unlike many other diabetes drugs, Rezulin doesn't lower blood sugar to dangerously low levels.

Diabetes specialists found Rezulin to be an effective addition to their treatment regimen for many diabetics. But over the course of the last three years, more liver abnormalities were noted. Warnings to physicians were added to the package label at the behest of the FDA on two separate occasions, advising physicians to utilize more frequent blood testing, and then restricting its use to those who did not benefit from other medications. Some doctors, however, failed to follow these directions assiduously.

In 1999, two similar agents for diabetes treatment were approved and marketed: SmithKline Beecham's Avandia and Eli Lilly & Co.'s Actos. Thus far, the liver toxicity that led to 63 deaths among those on Rezulin has not been found with these drugs.

Last week, as a result of standard post-marketing surveillance, the FDA sensibly requested Warner-Lambert to withdraw Rezulin, given the availability of the newer, safer agents. But this remedial action came too late to suit Sidney Wolfe of the Naderite group Public Citizen. He immediately criticized the FDA for having approved the drug in the first place. He argued that since FDA's fast-track procedure was initiated, dangerous drugs have been unleashed on the American
public, injuring patients. He went on to note that if the agency had acted earlier, as had authorities in Britain, some patients would still be alive.

But many diabetics would be sicker, or dead, without Rezulin, given that its two alternatives were not available in 1997 and 1998. That's the real lesson: Rezulin's unique benefits justified its risks. The risk/benefit ratio is as paramount when the FDA evaluates a medicine as when a physician prescribes one. The enviable health and longevity of the American people is in large measure attributable to the professionalism and responsibility of the FDA in evaluating our pharmaceuticals. Of more than 500 drugs approved since 1980, only 15 slightly more than 2% have been withdrawn.

The FDA rightly stands by its approval process on Rezulin. In its own defense, the agency makes an obvious but important point: All side-effects of a drug cannot possibly be detected in the small-scale clinical trials that precede mass-marketing. Rezulin was tested on 2,500 patients before release, and severe liver damage was not detected. Officials of the FDA's Clinical Drug Evaluation Center point out that Rezulin would not have been withdrawn even now were it not for the availability of newer, safer insulin-sensitizer drugs. But even the most thorough regulatory process will fail if the appropriate safeguards are ignored when a drug is mass-marketed. This is the responsibility of the treating physician.

To pontificate now that the drug should never have been approved amounts to Monday-morning quarterbacking. All drugs have risks, especially new drugs, and we often need the data from post-marketing surveillance to detect them. To shy away from releasing breakthrough drugs because of fear of unpredictable side effects would cripple a system that has benefited us immeasurably.