When is a drug too risky to stay on the market?

June 30 2010, By MARILYNN MARCHIONE , AP Medical Writer

(AP) -- The arthritis pill Vioxx was withdrawn but menopause hormones were not, even though both were tied to heart risks. A multiple sclerosis medicine was pulled and later allowed back on. So, when is a drug too risky to stay on the market?

Drug safety questions arose again this week, as calls mount for the diabetes pill Avandia to be withdrawn. Surprisingly, the Food and Drug Administration has no firm rules for deciding such cases - just a murky guideline of "when the risks exceed the benefits."

"Each drug has its own complex story," so comparisons to previous decisions can't be made, said Dr. Joshua Sharfstein, the FDA's principal deputy commissioner.

The agency does need better criteria for weighing drug safety, he said. It has asked a group of outside scientists, the Institute of Medicine, to give advice. A report is expected before the July 13-14 hearing on Avandia, a controversial pill whose maker, GlaxoSmithKline PLC, insists is safe.

The FDA can order a drug off the market, but that can be challenged in court. Usually, a company voluntarily withdraws the medicine at the FDA's request.

Many things influence whether such a request is made, said Dr. Brian Strom, a drug safety expert at the University of Pennsylvania. He is a longtime FDA drug safety adviser who has consulted for Takeda

Pharmaceuticals, which makes Actos, an Avandia rival.

Some factors to consider:

- How serious is the illness being treated? Severe side effects are accepted for cancer drugs, for example, but not for an allergy drug such as Seldane, which on rare occasions caused sudden death and was withdrawn a decade ago, Strom said.

- How big is the harm? "Causing a little nausea isn't so bad. Killing people is," Strom said.

- How frequent are the risks versus the benefits?

A large federal study was stopped in 2002 after researchers saw more breast cancers and heart problems among women taking estrogen-progestin pills. Yet the absolute risk of suffering one of these problems was relatively small, and hormones remain the most effective treatment for menopause symptoms.

The multiple sclerosis drug Tysabri was withdrawn because of a rare but serious side effect, then allowed to be sold again under a restricted distribution system. There are few drugs available to help people with that disease.

- Are there safer alternatives? This may prove to be the strongest argument for those wanting Avandia withdrawn. A new study this week found Actos - the only other drug that works the way Avandia does - to be safer.

The popular arthritis pill Vioxx originally won approval because it was a more powerful and safer alternative to painkillers that cause stomach troubles. That advantage disappeared when Vioxx's heart risks emerged,

and a drug without that problem, Pfizer Inc.'s Celebrex, was available. Merck & Co. withdrew Vioxx in 2004.

Many see a similar situation with Avandia and Actos. However, Sharfstein said one of the issues the Institute of Medicine had been asked to advise the FDA on is how to weigh comparison studies, especially if they are not gold-standard trials where similar groups of people are given one or the other pill and followed over time to see how each group fares.

"Avandia won't be decided in reference to Vioxx," Sharfstein said. "It will stand on its own."

The internal staff analyses of risks have not been released yet, and will shed more light on the situation, he added.

In Avandia's case, some but not all studies have tied it to heart risks and deaths, and the bottom line may be different for various age groups. A new study this week found risks among elderly Medicare patients not seen in younger ones.

Also, the drug initially won approval in 1999 because it lowered blood sugar. That's a less clear benefit than reducing kidney problems or other diabetes complications.

Questionable approval criteria now are coming back to haunt the FDA as harmful effects emerge for drugs already in wide use, said Dr. Alastair Wood. He is a longtime Vanderbilt University professor now at a private equity firm who has led many FDA drug safety panels.

"Ten years since the drug was approved and we still don't know if it produces the benefits that patients really want. That's unacceptable," he lamented.

Dr. Robert Califf, a heart research leader at Duke University, agreed.

"We've got these legacy drugs that are out there without clear evidence one way or another," because they were approved on "soft" criteria, he said.

Given that, it's hard to see how the FDA can push Glaxo to withdraw Avandia now, he said. The studies on risk "are all over the place," said Califf, who has consulted for the company.

The FDA has called the special meeting in July to hear from experts on its endocrinology and drug safety panels, which include physicians from leading hospitals and research universities.

Ultimately, though, the decision whether to withdraw the drug rests with federal scientists. In 2007, the agency's internal panel of drug safety specialists voted 8-7 to keep Avandia on the market.

The agency's drug safety panel, which consists of high-ranking officials from the FDA and other agencies, was set up in 2005 to resolve safety disputes, after the agency was criticized for its handling of the Vioxx situation.

It will likely include FDA drug center leadership who oversaw the initial approval and subsequent labeling of Avandia.

More information:
Food and Drug Administration: www.fda.gov
Diabetes drug comparisons:
www.effectivehealthcare.ahrq.gov/reports/final.cfm
Diabetes information: www.diabetes.org
diabetes.niddk.nih.gov/