



Drug Danger

By Scott Gottlieb, M.D.

An April 2007 recommendation by a Food and Drug Administration (FDA) advisory panel against approving the Merck painkiller Arcoxia—a drug already in use in sixty-three countries around the world—has dramatic implications for the future of drug research in this country. In effect, the agency is establishing new rules for approving drugs to treat some conditions for which other therapies exist, and you can bet drug companies are frantically re-examining their current research and development efforts.

The goal was once to continuously expand the pharmacopeia of available drugs, as long as each drug was safe. But, apparently, not anymore. In voting 20 to 1 to reject Arcoxia, the FDA's advisers said that for certain ailments we already have enough medicines. This decision will ultimately deny patients needed choices, reflecting a dangerous way of looking at drug development, safety, and, more importantly, the practice of medicine. Science is leading us toward matching specific drugs to specific patients, a therapeutic process that requires more drug variety, not less. The FDA may now be moving in the opposite direction.

Arcoxia is part of a class of medicines known as non-steroidal anti-inflammatory drugs (NSAIDs) that work by blocking a substance the human body produces to feel pain. The problem is that the human body uses a similar substance to protect the lining of the stomach. Arcoxia is designed to selectively block only the substance causing pain, sparing the stomach from some of the upset and even ulcers caused by older NSAIDs. Arcoxia cut the rate of ulcers and bleeding to 1 percent from about 2 percent in clinical trials comparing it to older NSAIDs, perhaps an important advantage for those susceptible to the stomach-related side effects.

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Treating Patients as Individuals

Asked about Arcoxia, one of the FDA's senior officials said that "simply having another drug on the market . . . didn't seem to be sufficient reason" for approval. But the fact remains that all drugs that are tweaks on other medicines have different profiles. Sometimes small changes can dramatically impact how a new drug performs. But more often the therapeutic differences are subtler, mattering only for subsets of patients who only respond well to one particular version of a molecule. This is why doctors sometimes cycle a patient through multiple drugs in a "class" of medicines before finding one that works well for that person.

Merck did a poor job explaining to the FDA that fine genetic differences lead some people to respond differently to similar drugs. Merck also ignored the FDA's advice on how to show these differential benefits. The company did not even offer a few patient testimonials to explain why Arcoxia could benefit a subset of those who do not find relief with existing medicines.

But this is no reason to be indifferent about Arcoxia's approval, because there are larger issues at stake here than whether or not Merck gets another drug to market. While the NSAIDs are well understood, when it comes to many other drugs it is going to be hard to specify before approval which subpopulation of patients might

benefit. Benefits to subpopulations typically require non-predefined analysis of large data sets—the kind of analysis that often comes after a drug is approved, not before. Requiring a new drug to show superiority for some people to existing treatments will ultimately lead to fewer therapeutic options.

Moreover, a lot of the misgivings about Arcoxia were not just over its similar benefits to existing drugs, but with concern that it could harbor the same risks of increased cardiovascular events as other NSAIDS without offering sufficiently new advantages. This is of a piece with an increasing focus on drug safety made manifest in renewed efforts to uncover ever subtler side effects, then add them to drug warning labels. Sometimes these efforts lead to keeping new drugs off the market altogether.

But this information does little to inform patients of their individual odds of having a bad outcome. There is not enough corresponding effort to find the correlations between safety observations and the underlying science that reveals why some people are prone to certain side effects and others are not. Patients are given little orientation to know what the information on warning labels means to them.

Pro-Choice

Patients need new drug choices, such as Arcoxia, even when the new drugs reveal the same side effects as the old

drugs. Equally important to surfacing side effects is revealing the science that explains why only certain patients will suffer them. The science to do these things is at hand.

Toward these ends, there is a drug safety bill in the Senate right now, sponsored by Sens. Edward Kennedy (D.-Mass.) and Michael Enzi (R.-Mont.), that contains

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some elements of what could emerge as a more systematic approach to tracking and evaluating drug safety. But like a lot of other efforts to “fix” the drug safety system, the legislation fails to envision how the science of drug response can be married to the monitoring of problems with medicines. The legislation instead relies too much on bureaucratic interventions called “risk management plans” that employ a heap of red tape to enable regulators to “manage” the use of individ-

ual drugs on a case-by-case basis to avoid side effects that the legislation wrongly assumes cannot be more fully understood.

Given the sheer size of trials Merck ran, few pain pills in Arcoxia’s class will be as closely examined and clearly understood. Yet in today’s political environment, precautionary principles will keep the FDA from letting patients choose if this pill is right for them. All drugs have risks that patients must weigh against the benefits. Limiting choices patients can make in seeking relief will not change that. But patients would be better off if the FDA focused on unearthing information to help doctors determine which pills will perform the best for each individual patient.