

Risk, Benefit and the FDA
by
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In September last year Merck & Co. pulled its popular and effective arthritis pain medication, Vioxx, from the market because researchers investigating the possible efficacy of heightened doses of Vioxx in the treatment of problems other than arthritis discovered that, at those heightened doses, the drug increased the probability of cardiovascular harms (heart attacks and strokes). In December one group of researchers investigating another popular and effective arthritis pain medication, Pfizer's Celebrex, again in heightened doses, and again for uses other than arthritis pain relief, also discovered a (very small) increased probability of cardiovascular harms. Another group of investigators doing the same research on Celebrex found no such heightened risk. Pfizer did not pull Celebrex from the market, but it did suspend all advertising of the drug directly to consumers.

Both Vioxx and Celebrex are COX-2 inhibitors, pain relievers that carry a significantly lower risk of causing gastro-intestinal bleeding than other arthritis pain medications such as Tylenol and aspirin. Arthritis sufferers who are very susceptible to gastro-intestinal bleeding have no place to turn for arthritis pain relief except to COX-2 inhibitors.

This has set off a maelstrom of negative commentary among journalists about COX-2 inhibitors, with the more dimwitted among them calling on the federal Food and Drug Administration (FDA) to ban all drugs in that class. Others worry that the FDA drug approval process is "broken" and conclude that it must be changed to make it much more difficult for drugs that later turn out to have harmful effects to be approved in the

first place. The FDA (also known as the Federal Drug Administration) has scheduled hearings for February 16 -18 to consider the safety of all COX-2 inhibitors. Given the personal incentives to which FDA regulators respond, they well might decide to ban the drugs. That would be a disaster for many arthritis sufferers.

FDA regulators can make two types of errors in making decisions about whether to approve a drug for the American market. Statisticians call them Type I and Type II errors, and they apply to most decisions people make. They are false positives and false negatives. FDA regulators can approve a drug that turns out to be harmful (a false positive) and can refuse to approve a drug that actually would be beneficial (a false negative). FDA regulators are more afraid of the false positive than the false negative error. Why? Because if they approve a drug that later turns out to be harmful, the harms become visible; photographers and journalists can chronicle the harms to identifiable victims and trace the harms back to the specific regulators that committed the error. Regulators are personally at risk of public ridicule or worse. If regulators decide to disapprove a drug that would have been beneficial, some people will be harmed, but photographers and journalists cannot chronicle the harm. One cannot take a picture of what doesn't happen. Who will ever know of the people who are not benefited because of a blunder by FDA regulators? In such cases regulators are likely to be applauded as appropriately cautious.

Letting a person take a bad drug can kill. Prohibiting a person from taking a good drug can also kill. When FDA regulators decrease the probability of committing a Type I error (approving a good drug) by making it more difficult to approve any drug, they thereby increase the probability of committing a Type II error (blocking a good drug).

FDA regulators should balance one type of error against another, but their personal incentive is to prefer Type II over Type I.

There is risk attached to taking any medication. Some risks are known and some aren't. It is our lot in life to make decisions under uncertainty. Adults of normal mental capacity should be allowed to make such decisions for themselves. In the case of prescription medications physicians should be free to make decisions about whether to prescribe a drug, and patients should be free to decide whether to take it. Prudent decisionmakers seek appropriate knowledge before making decisions, but there is no such thing as perfect knowledge. We are not obviously better off by letting distant third parties, biased in favor of a particular type of error, make such decisions for us.

Alas, the COX-2 inhibitor scare is likely induce the FDA do more harm than it otherwise would. FDA regulators will likely ignore the fact that the newly discovered harms associated with Vioxx and Celebrex resulted from doses far above those safely used for effective arthritis pain relief. When the game is CYA, the regulators don't give a damn about victims of Type II errors.