Max Abramowitz Reif and Kyle Robles

12-1-10

ECS 188

2124 words

Drug Safety and the FDA

Throughout America's history of a capitalist economy and the free market sale of goods, the regulation of the production and sale of drugs has always been a contentious issue. While most of the drugs on the market today are sold as cures or aids to various ailments or diseases, some of these products are not the wonderful remedies that they advertise themselves as: some come with a range of serious side effects, others do not cause the good that they are intended to, and a few are overprescribed in order to make a profit. However, none of these problems with modern medicine are freshly arisen or even unforeseen; all of these issues have been prevalent throughout the history of man-made medicine.

It was for these and other problems with the pharmaceutical field that catalyzed the creation of the US Food and Drug Administration in 1906, an agency of the US department of Health and Human Services, which was designed to control and regulate the aforementioned problems through thorough testing and inquiry into each new proposed drug before it could be released onto the market for human consumption. However, even the FDA has problems of it's own. Recently, several drugs which were passed by the FDA were found to be severely harmful and even deadly, and their drug screening process and even the ethics of those undertaking the testing have been thrown into question. Although the FDA is a necessary part of our society and still does more good than harm, it is in no way a perfect system and it still has many significant flaws which need to be fixed.

The precursor to the FDA was put into place in 1906 when the Food and Drug Act was signed into law by president Teddy Roosevelt. While this act did not directly create the regulatory agency, it did outlaw the manufacture, sale, or transportation of adulterated food products and poisonous patent

medicines, and gave the US government the power to stop and sale and seize any of these harmful goods or mislabed and falsely advertised drugs. However, this still allowed the sale of many harmful substances, such as radioactive drinks and cosmetics which caused blindness, so in 1938 the Food Drug and Cosmetics Act was passed which allowed the FDA to inspect and regulate all food and drug substances before they were put onto the market. This act was meant to insure the safety and health of the American people and is a cornerstone of what the FDA still does today.

To create an understanding to build our analysis on let us begin with a look at the approval process of the FDA. According to the main site of the FDA, the drug development and approval process for prescription and nonprescription drugs is handled by the FDA's Center for Drug Evaluation and Research (CDER). The process starts in the hands of the company with the newly developed drug. When a company develops any type of drug and want to release it into the public market they must first test their product according to safety regulations. After testing and compiling data which shows the effectiveness and safety of their product, this data is sent to the CDER and put under review by the FDA's own group of chemists, physicians, pharmacologists and other specialized. To make matters clear, effectiveness of a product refers to how well the said product does in regards to what its purpose is. This does not imply that the product must do better than currently approved products with the same purpose. Safety regulations for drugs are also reviewed with constantly changing standards based on up to date scientific research.

Supposing that this is indeed a rigorous process with extensive testing and reviewing, how is it possible that dangerous products still manage to slip by? One such path is through off label prescriptions. In this case drugs are used by consumers in ways not approved by the FDA. During the review process, a drug may be released under the approval for the treatment of one type of condition. However there is nothing legally wrong with doctors prescribing an approved drug to treat other conditions. In this case, is it the fault of the FDA should an accident occur or does the fault lie with the

physician distributing the drug?

It isn't even the case that off-label prescriptions are rare. According to a survey referenced in an article written by Alexander T. Tabarrok, in the case of cancer patients over a third of them were given off-label prescriptions while over half were given non-FDA approved prescriptions. Similarly in the case of AIDS patients, 81 percent were found to take at least one drug off-label.

One may ask why there is such a high frequency of off-label prescriptions. This happens due to the nature of the medical field. As soon as new cures are discovered, the FDA lags behind in approving these new cures for active use. This is especially true in the case of terminal diseases as a patient would usually desire the most innovative treatment possible since they are fighting a battle of time. In this given situation, any physician would be facing quite the moral dilemma of choosing between two options; Allow treatments at the risk of later side-effects due to undiscovered problems with the medication or allow patients to die as a potential cure goes through the process of approval. This dire need for the latest treatments combined with the FDA's long process of approving drugs is a potent combination in pushing doctors toward off-label prescriptions.

In 1999, the FDA gave the Merck cooperation the go ahead to start selling a pain medication called Rofecoxib, which was sold under the brand name Vioxx. Vioxx went though all the normal FDA pharmaceutical testing and was deemed safe for the American public. However, after the drug had been on the market for several years, a group of Merck researchers decided to run some tests on the drug to discern if Vioxx had any significant use as a polyp prevention drug. What they found was that in fact taking Vioxx for over 18 months greatly increased the users risk of heart attack, stroke, and other cardiovascular illnesses. While Merck was not majorly concerned with the results of this study, other data surfaced over the next year that led to the same conclusion. The accumulation of this data caused pressure to be put on Merck, which eventually led to Merck voluntarily pulling Vioxx from the market in September 2004. However, there were many independent groups which have said that Merck knew

of the dangers of Vioxx earlier, but did not pull the drug until others had learned of its potential danger, which put millions in harm's way. FDA analysts estimated that Vioxx caused between 88,000 and 139,000 heart attacks, 30 to 40 percent of which were probably fatal, in the five years the drug was on the market. But after the dust had settled on this case there still remains a looming question: How was Vioxx passed by the FDA in the first place? Isn't this the exact type of thing the FDA was designed to catch in order to keep the American public safe? Even more disconcerting, this was not the only deadly drug the FDA has let onto the market.

The drug flecainide was first created by the 3M company in the early 80s, and in early non human trials showed to be a very effective drug for the treatment of irregular heartbeats. Seeing these results, 3M sensed the potential for a new wonder drug and quickly pushed forward for human testing and for FDA approval. However, the effectiveness 3M had seen in the non human trials of flecainide did not match the results of the human testing, and even worse, a small portion of the human trial had died. However, with the influence 3M had within the FDA and the millions of dollars they had already sunken into this drug, they heavily lobbied the FDA for flecainide's approval for sale, and they got it in 1986. In 1989, after flecainide had been on the market for over two years, the results of a medical study know as the Cardiac Arrhythmia Suppression Trial (CAST), which was conducted by the National Heart, Lung, and Blood Institute, a non partisan source, showed that patients with structural heart disease (such as a history of MI (heart attack), or left ventricular dysfunction) and also patients with ventricular arrhythmias, had a significantly increased risk of death when they took flecainide, which at the time was being prescribed for certain heart arrhythmias with warning of the potential danger. Since the CAST showed a 3.6 fold increase in the death rate for these patients, many warnings and precautions have been adhered to flecainide, but it remains available for purchase in the USA. However, this incident was the subject of a book in 1995 called *Deadly Medicine*, in which author Thomas Moore asserts that 3M knowingly put a dangerous drug onto the market without any

precautions and used it's influence to force the FDA to accept it, and as a result of such between 50,000 and 200,000 people may have died as a direct result of taking flecainide. However, none of these allegations have been proven in a court of law, but nonetheless this test study brings up the question as did the Vioxx case: How did this drug pass through the FDA testing without a serious warning in the first place?

With these cases of slip ups under the FDA, one questions whether or not this process is really thorough. In a recent article by Doctor Alastair Wood in the New England Journal of Medicine, he suggests a four part approach to changing the current model of the FDA system. For the purposes of this paper, we shall look at the first two as the latter two are aimed to improve availability of drugs to combat higher level disease such as Alzheimer's disease or osteoarthritis. Wood's first point directs a change to the current status of long term safety data. As of now, drug manufacturers show the safety data for relatively short periods of time with little to no data on the long term effects of those using the drug. Wood suggests that under FDA supervision, drug manufacturers should be allowed to do tests to predict these long term effects of their products. The process would begin with the short term data being presented to the FDA. Should this data be found acceptable the manufacturer would be given a special status for a limited time to undergo further tests, which are approved and regulated by the FDA, to establish the long term effects of the product. If long term safety data is not complete or up to regulation by the given time, the manufacturer would lose their status. This change should encourage the development of safer drugs that are better understood in the long run of their usage.

Wood's second change addresses the use of phase 4 commitments, which are agreements by a manufacturer to perform further studies after their product gets an accelerated approval. According to Wood, the current system is faulty as manufacturers are not given penalties for not meeting their phase 4 commitment. Wood suggests that a shorter more limited status should be given for thus with a phase 4 commitment. If manufacturers produce data up to standard by the end of this time period, then they

shall receive an extension to conduct more research to further confirm the safety of their product. Those who do not meet these requirements for phase 4 by the given time period should then be dropped from phase 4 status.

Impact of the Food and Drug Administration Approval of *Flecainide* and *Encainide* on Coronary Artery Disease Mortality: Putting *Deadly Medicine* to the Test, Jeffrey L Anderson MD, American Journal of Cardiology, March 19 1996 http://www.ajconline.org/article/S0002-9149%2896%2900673-X/

Panel: FDA needs more power, funds, Diedtra Henderson, Boston Globe, September 23 2006, http://www.boston.com/business/healthcare/articles/2006/09/23/panel_fda_needs_more_power_funds/

Canadian and US Drug Approval Times and Safety Considerations, Nigel SB Rawson, PhD, The Annals of Pharmacotherapy, 2003, http://www.theannals.com/cgi/content/full/37/10/1403?ijkey=f4ec5d0438dbbc42fb8f21f4dccc9c3c6b4be7db

Gaps, Tensions, and Conflicts in the FDA Approval Process: Implications for Clinical Practice, Richard A. Deyo, MD, MPH, Journal of the American Board of Family Medicine, July 2 2003, http://www.jabfm.org/cgi/reprint/17/2/142

A Proposal for Radical Changes in the Drug-Approval Process, Alastair J.J. Wood, M.D., The New England Journal of Medicine, August 10 2006, http://www.nejm.org/doi/full/10.1056/NEJMsb055203

From Idea to Market: The Drug Approval Process, Martin S. Lipsky, MD, and Lisa K. Sharp, PhD, Journal of the American Board of Family Medicine, January 18 2001, http://www.jabfm.org/cgi/reprint/14/5/362

Development and Approval Process (Drugs), US Food and Drug Administration, http://www.fda.gov/drugs/developmentapprovalprocess/default.htm, http://www.fda.gov/default.htm