Providence College

DigitalCommons@Providence

Annual Undergraduate Conference on Health and Society

Fourth Annual Undergraduate Conference on Health and Society

Mar 23rd, 1:45 PM - 3:00 PM

Ethical Issues in the Drug Approval Process

Meghan McInnis
Providence College

Follow this and additional works at: https://digitalcommons.providence.edu/auchs

 Part of the Health Policy Commons, and the Policy Design, Analysis, and Evaluation Commons

McInnis, Meghan, "Ethical Issues in the Drug Approval Process" (2013). *Annual Undergraduate Conference on Health and Society*. 1.
https://digitalcommons.providence.edu/auchs/2013/panelc1/1

This Event is brought to you for free and open access by the Conferences & Events at DigitalCommons@Providence. It has been accepted for inclusion in Annual Undergraduate Conference on Health and Society by an authorized administrator of DigitalCommons@Providence. For more information, please contact dps@providence.edu.

Meghan McInnis
December 7, 2012
Health Care Reform Issue Paper

Ethical Issues in the Drug Approval Process

"I'm disappointed the commissioner has chosen to take the hardest line possible . . . for some women, the decision was nothing short of a death sentence"
- Terrence D. Kalley, husband of woman taking Avastin. *The New York Times* (Pollack 2011)

"It is the right decision for women and for science. We all wished the drug worked. It does not"
- Frances M. Visco, president of the National Breast Cancer Coalition. *The New York Times* (Pollack 2011)

Americans have been led to believe that a pill can cure everything and anything. Any pain, discomfort, affliction, or allergy can be fixed or alleviated with one small tablet. What happened to "An apple a day keeps the doctor away"? Today, Americans want to see their doctors in order to receive prescriptions for drugs. With so many drugs on the market it is important to pay attention to how these drugs are being produced and the regulated trials they must undergo before they can be released to the public. Clinical trial research is used in order to test the safety and efficacy of new medical treatments. By nature, clinical trial research involves human subjects, which means that ethical issues will always exist. One of the current ethical debates surrounding the drug approval process is the growing tension between making sure drugs are safe and the speed at which drugs can be sent to market. Proponents of safety argue that drug approval is not something that should be rushed, while proponents of speed argue that the faster drugs make it to market, the more lives that will be saved because people can actually use them. The case studies of Vioxx and Avastin illustrate the ethical and practical dilemmas in the drug approval process. I argue that new drugs for terminally ill patients, for which no better known treatment exists, should be made available to those patients as quickly as possible, including using streamlined approval, provided that patients are made clearly aware of the difference between research and treatment.

The Origins of Expedited Review

The age of expedited development and accelerated approval of new drugs began in the 1980s as a reaction to the emerging AIDS epidemic. Before this time, as mandated by the 1962 amendments to the Federal Food, Drug, and Cosmetic Act (FFDCA), all new drug applications had to undergo three phases of clinical trials and had to be approved by the Food and Drug Administration (FDA). It was estimated that this process took an average of eight years to complete and cost more than 50 million dollars per drug (Greenburg). While the new drug approval process was time consuming and costly, the 1962 amendments were welcomed at the time because of concerns about thalidomide. Thalidomide was a drug that a German pharmaceutical company had marketed as a sleeping pill, but was later found to be associated with the birth of thousands of malformed babies in Western Europe (Promoting Safe and Effective Drugs for 100 Years 2006). Although the Medical Officer of the FDA had fortunately kept thalidomide off the U.S. market, the American public was eager to support stricter regulations on pharmaceutical companies. When the AIDS epidemic began to grow, becoming the leading cause of death for U.S. men ages 25-44 in 1992, FDA regulations designed to protect patients, by properly evaluating risks and ensuring that new drugs were safe before they were released to the public, became seen as a hindrance to progress and a suppression of patient autonomy (Anderson 2011). The ethics of the entire drug approval process became very different when patients, such as those with AIDS, were terminally ill: "Terminally ill patients lacking effective conventional treatments confront a risk-benefit determination very different from that of the general public. Such patients have far greater incentives than the larger public to gather their own information and to take risks" (Greensburg). AIDS patients utilized these incentives and began to organize. Organizations, including the Gay Men's Health Crisis started in 1982,

and the AIDS Coalition to Unleash Power (ACT UP) established in 1987, led protests and demonstrations in order to pressure the FDA into changing its policies. In response to this pressure, the FDA adopted many new drug approval reform measures, including "Treatment IND (Investigational New Drug)" and "Accelerated Approval" regulations. "Treatment IND" regulations, promulgated in 1987, made experimental drugs available to patients, physicians and manufacturers when certain conditions were met, including that the drug was designed to treat a serious or life threatening condition and no other treatment options existed (Greenburg). "Accelerated Approval" regulations, instituted in 1993, built on previous "Subpart E" regulations, which enabled early and constant collaboration between the FDA and a pharmaceutical company developing a life saving drug so that Phase III Trials could be bypassed if enough information was gathered. The "Accelerated Approval" regulations allowed "surrogate endpoints", or intermediate biochemical effects of a new drug, to be used as a final basis for FDA approval, provided that post-marketing studies were pursued to ensure effectiveness and safety (Greensburg). Therefore, life saving drugs can be approved for treatment based on one clinical effect. In 1997, Congress codified the FDA's accelerated approval regulations by enacting Section 506 of the Federal Food, Drug and Cosmetic Act (Decision of the Commissioner 2011).

The ramifications of these new regulations were far reaching, affecting far more than just the AIDS population. They opened the door for further debate about whether or not the FDA regulations expedited the approval process too much, compromising patient safety, or whether the regulations should be stricter in ensuring patient safety is met prior to sales. The two drugs that will be described in this paper serve as tangible examples of this controversy. Vioxx, a pain-reliever for arthritis approved by the FDA in 1999, was pulled from the market five years after

being released because it was shown to cause an increased risk of serious cardiovascular events. Avastin, a drug used to treat several types of cancers, was granted accelerated approval by the FDA in 2008, under the regulations developed in 1993, to treat metastatic breast cancer, but later had this early approval revoked. Both cases highlight the pros and cons of the expedited approval process, which will be discussed in greater detail in the rest of the paper. The Vioxx recall highlights (1) the ethics of clinical trial research itself, (2) the evaluation of risks versus benefits of any new treatment, (3) the growth of Contract Research Organizations (CROs) and (4) the ethics of post-marketing research. The Avastin story contrasts the lessons learned from the Vioxx recall, specifically the evaluation of risks versus benefits. I use these contrasting issues to support my argument that expedited approval is ethical and should be used to get drugs to terminally ill patients as quickly as possible, provided that patients are made clearly aware of the difference between research and treatment.

Vioxx

Merck is a successful global pharmaceutical entity that has much experience in the field of drug development. In 2009, Merck was ranked second of the top fifteen Global Pharma Corporations, falling only behind Pfizer (Pharma and Biotech Industry Global Report). By May of 1999, Merck had successfully completed the development, testing and proper marketing of a new drug to treat arthritis pain, Vioxx. Vioxx was an important drug for Merck because it was to compete with Celebrex, Pfizer's new drug to treat arthritis pain. Additionally, the Vioxx sales came at a pivotal time for Merck because patents to four of their major drugs were scheduled to expire in 2000 and 2001, meaning that generic equivalents would be allowed to enter the market and consequently depreciate Merck's sales (Presley). Vioxx "was crucial for Merck's bottom line – the high-margin blockbuster prescription drug contributed a fifth of Merck's profits in

2003" (Oberholzer-Gee 2004). On May 20, 1999, the FDA approved Merck's application for Vioxx to be brought to market (Presley). As soon as Vioxx was released, it was an instant success: "By the end of 1999, over 5 million prescriptions had been written for Vioxx and it had been launched in 47 countries" (Presley). This was more than 22,000 prescriptions per day and was mainly because Merck successfully marketed Vioxx to physicians (Presley). Merck desired to market Vioxx so heavily because the population was aging and the arthritis market was booming. In 1999, analysts expected the market for prescription arthritis drugs to rise from $7.2 billion worldwide to $13 billion by 2005 (Morrow 1999). Despite gaining FDA approval and huge economic success, Merck continued to test Vioxx in post-marketing studies during and after its release to see if it had other uses. These post-marketing studies eventually came to highlight serious health concerns that would lead to Merck pulling Vioxx from the market.

In January of 1999, just months before Vioxx received FDA approval, Merck began a set of clinical trials known as VIGOR (Vioxx Gastrointestinal Outcomes Research) to test the efficacy and safety of Vioxx compared to its top competitor, Aleve. The goal of the VIGOR trials was to compare the gastrointestinal outcomes of patients taking Vioxx (Group A) versus those in patients taking Aleve, generically known as naxopren (Group B) (Presley). Merck was not forced to pursue these trials, but chose to perform them because the FDA had the power to approve what the contents of the Vioxx label. "Although the FDA has limited power to compel firms to conduct post-marketing studies, it must approve the labeling for drugs, and it has the authority to issue a public health advisory or even recall a product with adverse effects from the market, giving it some leverage with manufacturers" (Eisenburg 2005). Merck opposed a study that focused solely on cardiovascular risks, but decided "in consultation with the FDA, to monitor data on these risks in ongoing studies of new indications, thereby signaling optimism

about new markets rather than concern about side effects" (Eisenburg 2005). Merck was not alone in conducting post-marketing research, but post-marketing studies are more common now than they were in 1999 due to federal legislation passed in 2007 that strengthened the authority of the FDA in the post-marketing period. Merck's VIGOR trial involved 8,000 participants and was monitored by a Data Safety and Monitoring Board (DSMB) (Presley). The DSMB noticed an increased number of serious cardiovascular events in Group A than Group B, 52 compared to 29, but they did not know originally whether this was because Group A had received a negative side effect or Group B had received a protective side effect. The DSMB requested additional safety analysis reports on the cardiovascular events that had occurred before the study was to be published. However, these safety concerns were pushed aside by top Merck officials who were more concerned with their stakeholders and the fact that Vioxx was their top selling product. For example, the President of Merck Research Laboratories, admitted that "safety risks were evident, but he hoped that Merck could present the risks as a class effect, or, in other words, present the risks so that they appeared common to all drugs that function as COX-2 inhibitors" (Presley). Merck was not willing to let one set of trials dictate the future of Vioxx without putting up a fight.

Before the results of the VIGOR trials were even published, Merck's Marketing and Sales team published a statement claiming that the main results of the study were that Vioxx produced a significant reduction of serious gastrointestinal events compared to Aleve, generically known as naproxen, in patients being treated for rheumatoid arthritis (Presley). The statement tried to avoid any concern about increased risk of serious cardiovascular events in patients taking Vioxx by attributing the increase to a health benefit received in patients taking Aleve: "In addition, significantly fewer thromboembolic events were observed in patients taking

naproxen in this GI outcomes study, which is consistent with naproxen's ability to block platelet aggregation" (Presley). Merck attempted to attribute Vioxx's inability to block platelet aggregation as an effect common to all COX-2 inhibitor drugs, even before the study results were released to the public. On November 23, 2000, the results published in the *New England Journal of Medicine* showed that patients taking Vioxx were five times more likely to experience an adverse cardiovascular event than patients taking Aleve (Presley). The Marketing and Sales team continued to be relentless in trying to divert attention and keep the media from catching on to the story. For example, they created a reference manual for all their field representatives to follow that included a list of tough questions physicians might ask about the study results and a set of talking points they could respond with. Even after an FDA committee and a *New York Times* article noted the increased risks of cardiovascular events and questioned the safety of Vioxx, Merck continued to stick to its original conclusion that it was due to a protective effect of naxopren and that Vioxx was still more advantageous than narcotics for pain management. Safety concerns continued to grow however, and eventually Merck was forced to make a decision. Merck had continued to test Vioxx in clinical trials for its effects on Alzheimer's disease and colon polyps. However, these studies also revealed safety concerns associated with Vioxx. Merck requested an emergency meeting with the FDA on September 28, 2004 to share the data gained from these additional studies. In collaboration with the FDA, on September 30, 2004, almost five years after the original safety concerns had first emerged, Merck decided to pull Vioxx from the market (Presley).

The fact that Merck knew all along about the increased risk of serious cardiovascular events in patients taking Vioxx, but continued to sweep the information to the side as they promoted their blockbuster drug, shows that FDA regulation is necessary. If the FDA had not

been regulating Merck, they would have continued to market Vioxx worldwide in attempts to increase their bottom-line, despite the adverse side effects to patients. The expedited approval process should be used to bring drugs to market as quickly as possible, as long as appropriate regulations, which keep pharmaceutical companies in check, are in place.

Effects of the Vioxx Recall: Clinical Trial Research

The Vioxx recall raises several issues about the drug approval process. The first issue is whether or not clinical trial research itself is ethical. The use of randomized trials began in the early 1950s when streptomycin was evaluated in patients with tuberculosis (Passamani 1991). Since then, the process of clinical trials has been greatly revised and refined. In an article in *The New England Journal of Medicine*, Dr. Passamini, a doctor from the National, Heart and Lung Institute, makes a strong case that clinical trials are the most scientifically and ethically sound way to test new drugs (Passamani 1991). He argues that randomized trials, as compared to observational studies or a trust in common sense, are the most effective way to prove the safety and efficacy of a new drug. He believes that in order to be ethical, clinical trials need to obtain informed consent from all patients, give patients the ability to end the study at any time and make the patients clearly aware that they are part of an experiment. Additionally, a state of clinical equipoise must also exist. This occurs when "a community of competent physicians would be content to have their patients pursue any of the treatment strategies being tested in a randomized trial, since none of them has been clearly established as preferable" (Passamani 1991). In the case of the VIGOR trial, neither Vioxx nor Aleve had been shown to be preferable for treatment of gastrointestinal issues. Physicians could rightfully and ethically recommend their patients take part in this trial because the benefits would outweigh the risks, especially since neither group would be receiving a placebo. Passamani notes that one of the common

counterarguments is that clinical trials are not ethical because physicians sacrifice the interests of their current patients to the interests of all future patients when they ask patients to participate in a clinical trial. Passamani argues that this perspective is wrong because in recommending a clinical trial as treatment, physicians rightfully weigh the evidence of known therapies versus the data that exists about the possibility of new treatments. When treatments have not shown to be preferable, it is not unethical to have patients participate in clinical trials in order to assess their efficacy. For terminally ill patients, this becomes an even stronger argument. Terminally ill patients have a greater incentive to participate in clinical trials because it may be the only treatment option they have. The clinical trial research process should be expedited for drugs designed to treat terminally ill patients with no other research options.

Effects of the Vioxx Recall: Evaluation of Risks vs. Benefits

Although Passamani demonstrates that the concept of clinical trial research is ethical, the Vioxx recall raises ethical issues that Passamani fails to consider. For example, Passamani does not consider the question of what should be done with the information gained from a trial after the trial is completed. In the VIGOR trial, 52 cases of serious cardiovascular events were found in the group taking Vioxx. The issue becomes not whether that information was gained ethically, but how that information should be interpreted and used in an ethical manner. Is the risk of developing a serious cardiovascular event enough to outweigh the benefits of pain and gastrointestinal relief? Vioxx was shown to cause increased risk of cardiovascular events among certain older patients, but successfully reduced pain due to arthritis in many others. While the relative risk for having a heart attack was higher among patients taking Vioxx versus those taking Aleve, 0.4% compared to 0.1%, the absolute risk remained how. However, "because tens of millions of people in more than 80 countries took Vioxx, this small risk translated into an

important public health issue" (Greener 2008). It remains up for debate whether Vioxx should have been pulled from the market. Mark Pauly, a professor at the University of Pennsylvania, believes that the Vioxx recall highlights "the inherent tradeoff between the health benefits of taking any drug and the risk of side effects" (Vioxx and Other Painkillers). He makes the point that the issue with all new drugs is that, "as more people take the drug, more information about side effects is likely to come out. But as more people take the drug, it grows more important to a firm's profitability" (Vioxx and Other Painkillers). Vioxx sales reached $2.5 billion in 2003 (Vioxx and Other Painkillers). Millions of people were taking the drug, making it more likely for adverse side effects to be noticed. Merck had strong incentives not to publicize the information gained from the VIGOR trial though because it would severely cut into Merck's sales. However, just because a drug is shown to have risks of adverse side effects does not necessarily mean it has to be pulled from the market. Pauly points out that, "If all drugs were pulled from the market based on the appearance of side effects, there would be no vaccinations for childhood diseases that once were killers, or for medications to treat HIV/AIDS" (Vioxx and Other Painkillers). All drugs have side effects and risks associated them. The FDA made the judgment call that the risks of Vioxx were too severe and outweighed the benefits. While the FDA made an ethical decision in this case because patients were protected from the risk of serious cardiovascular events and could simply switch to another arthritis drug, such as Celebrex, it would have been an unethical decision if it was the only-life saving drug available to terminally ill patients. When patients are terminally ill the evaluation of risks and benefits changes significantly. As those with AIDS argued in the 1980s and 1990s, expedited approval should be used for terminally ill patients because even a small benefit could merit use, despite high risks.

Effects of the Vioxx Recall: CROs

The latest trend in clinical trial research, and another ethical issue surrounding it, is the growth of Contract Research Organizations (CROs). The CRO industry emerged in its current form in the 1970s and 1980s. However, the CRO industry took off in the 1990s, "rising from 4% of R&D spend in the early 90s, to pushing 50% in the mid 2000s" (Walsh 2010). In 2007, there were more than 1000 CROs in operation globally and the top four were billion dollar companies (Schuchman 2007). The top 10 companies control 56% of the market (Walsh 2010). CROs have surpassed academia in clinical research because they can develop and test new drugs with greater efficiency. CROs represent one-third of total pharma and biotech spending on drug research and development (Brooks 2011). However, questions have been raised about the ethics of CROs because "annual CRO-industry revenues have increased from about $7 billion in 2001 to an estimated $17.8 billion today" (Schuchman 2007). In 2010, CRO revenue was projected to total $20 billion (Brooks 2011). Aside from the growing profits, critics are concerned about the speed at which CROs complete research studies. One argument is that quality suffers when more emphasis is placed on speed. Pierre Azoulay, an economist at the Massachusetts Institute of Technology's Sloan School of Management, describes CROs as "'data-production sweatshops,' where 'everyone's very focused on the data,' rather than on the totality of the knowledge required to determine whether a drug is worth pursuing further, and where 'all the incentives are to do [the work] fast'" (Schuchman 2007). However, a study done by Tufts found that CROs still turned out high-quality research (Schuchman 2007). CROs highlight the major flaws and strengths of the drug development industry today. While too much emphasis on speed and deliverables can serve to harm patients and violate ethical standards, when it comes to developing drugs for diseases that leave patients terminally ill, speed is essential. Because CROs break the trial process down into manageable concrete steps and emphasize swiftness at each

step, they are able to produce drugs faster than traditional academic research centers (Schuchman 2007). I believe CROs and their focus on speed need to be utilized for the development of drugs used to treat terminally ill patients. Terminally ill patients generally have few or no other viable treatment options. The possibility that a new drug will work, even if it has side effects that are found later, is enough reason to push drugs through trials as quickly as possible.

CROs also highlight the issue of whether the FDA has stringent enough regulations within the drug approval process or whether these regulations are more burdensome to the process than they are helpful. One of the criticisms of CROs stems from the fact that they are not well regulated by the FDA. Since many of the drug regulations that exist were written in the 1970s before the CRO industry emerged, they do not address CRO accountability (Schuchman 2007). A pharmaceutical company or sponsor hires a CRO to perform clinical trials, increasingly abroad, so that the company does not need to directly provide staff for and organize the trials. Therefore, CROs often report any issues found during a trial directly back to the drug company that hired them, not to the FDA. However, in turn, drug companies do not always report the issues to the FDA. It is unclear where the responsibility for ethical or safety issues falls in these cases. Additionally, CROs are even harder to monitor when their trial sites are increasingly being sent overseas, where research subjects are more available and less costly (Schuchman 2007). Many argue that CROs should be more heavily regulated, especially since their main focus is on speed.

Effects of the Vioxx Recall: Post-Marketing Research

The Vioxx recall serves as an example of the necessity of FDA regulations and the benefits of post-marketing research. While some could argue that the FDA failed to properly regulate Vioxx because the drug should never have gone to market in the first place, I agree with

the argument that the Vioxx recall should be viewed as a regulatory success story (Eisenburg 2005). This argument hinges on the fact that drugs resemble information products, such as databases, more so than other chemicals (Eisenburg 2005). The goal of clinical trial research is therefore information on the efficacy and safety of the drug. Pharmaceutical companies have powerful incentives to selectively share the information gathered from clinical trial research. However, "FDA regulation constrains these impulses by providing oversight of trial design, scrutiny of results by FDA scientists and outside experts, and assurance that marketing claims correspond to underlying data" (Eisenburg 2005). In terms of Vioxx, the FDA had limited power to actually mandate Merck to conduct post-marketing research trials, but Merck was constrained by regulations on off-label marketing and therefore had to pursue further studies after Vioxx was already approved for use of arthritis pain. Post-marketing research is valuable in that it can be used in conjunction with expedited approval. After expedited approval of a new drug, post-marketing research can be to gather further data on the safety and efficacy of the drug or replace one of the bypassed preliminary trials. In this way, drugs can be brought to market sooner and the trials will simply be completed after. The Vioxx recall demonstrates that post-marketing studies are beneficial in that they can find new uses of the drug or find adverse side effects that may have been missed, overlooked or underplayed before. Additionally, since post-marketing studies do not slow down the speed of the drug approval process, they can effectively be used to get drugs to terminally ill patients as quickly as possible.

Final Judgment on the Vioxx Recall

The FDA was justified in their decision to require Merck to recall Vioxx from the market. Evidence from several clinical trials showed that patients taking Vioxx had an increased risk of developing a serious cardiovascular event compared to other pain-relievers. Critics argue that

because these adverse effects were only seen in certain segments of the patient population, the FDA should simply have required these increased risk factors to be added to the Vioxx label. However, the FDA based its decision on reliable evidence and did so to protect the population as a whole. Additionally, since Vioxx is only a pain-reliever and not a life-saving treatment, following the recall patients could easily switch to a new drug, since there were many others available on the market. The FDA's decision to take Vioxx off the market did not prevent patients from receiving treatment for their condition. Instead, it served to protect the millions of patients who were taking Vioxx, because the increased risk of serious cardiovascular events was undeniable. David Graham, Associate Director for Science and Medicine at the FDA's Office of Drug Safety, "estimates that Vioxx caused between 88,000 and 138,000 additional heart attacks or sudden cardiac deaths in the USA, and that 30–40% of patients who suffered cardiovascular problems because of Vioxx probably died" (Greener 2008). The FDA used its regulating powers appropriately by recalling Vioxx from the market. In this case, the increased risks were not worth the benefits. In the case of Avastin, it is a different story.

Avastin

Developed by Genetech, Avastin is an antibody that inhibits the biological activity of a protein important in the formation of blood vessels. On February 26, 2004, the FDA's Center for Drug Evaluation and Research (CDER) approved Avastin as treatment to be used in combination with chemotherapy for patients with colon and rectum cancer. On February 2, 2008, CDER granted accelerated approval to Avastin in combination with paclitaxel as a treatment for patients who have not received chemotherapy for metastatic HER2-negative breast cancer (Decision of the Commissioner 2011). Approval was based on the results of E2100, a cooperative group randomized trial that showed a 5.5-month increase in progression free survival (Carpenter 2011).

The drug was granted accelerated approval solely on the basis of an increase in progression free survival because of the high case fatality rate of this type of cancer. Metastatic breast cancer is currently an incurable disease and over 90% of patients diagnosed with metastatic breast cancer die from it (Decision of the Commissioner 2011). For incurable diseases, prolongation of life remains the gold standard for approval of treatments. After FDA approval, Avastin became one of the top drugs for treating cancer. The breast cancer market totaled $8.6 billion in 2011 and is estimated to rise steadily to $10.9 billion in 2018 (Growth in the Breast Cancer Drug Market). In 2009, Avastin generated $4.8 billion in annual sales (Herper 2009). Roche, a Swiss pharmaceutical company, payed $47 million in March of 2009 to buy the part of Genetech that they did not already own because of its blockbuster drug Avastin. Genentech's projections had U.S. Avastin sales quadrupling to $10 billion by 2015 (Herper 2009).

However, Avastin sales fell short of this estimation, in part because the FDA revoked its accelerated approval to treat metastatic breast caner. On November 16, 2009, Genetech submitted the results of two additional trials, AVADO and RIBBON1, to the FDA in order to apply for regular approval of Avastin to treat metastatic breast cancer. On the basis of the results of these confirmatory trials, the FDA can either grant regular approval or revoke the accelerated approval. The FDA generally decides to revoke the accelerated approval if the additional trials fail to provide evidence that the drug is effective for the indications for which it was approved or fails to show that a clinical benefit justifies the risks associated with the use of the product for that indication. Both trials failed to confirm the 5.5-month increase in progression free survival found in the original E2100 study. AVADO showed an improvement in median progression free survival of 0.8 months, while RIBBON1 showed an improvement in median progression free survival of 1.2 months. Furthermore, neither study demonstrated that adding Avastin to

chemotherapy provided a benefit to overall survival. In addition, patients in the AVADO study self-reported that Avastin did not provide an improvement in quality of life (Decision of the Commissioner 2011). The FDA decided to revoke Avastin's accelerated approval because the trials failed to demonstrate that the drug was effective and that the clinical benefits outweighed the risks. In his final decision on the case, the Commissioner of the FDA stated: "As results from these studies have come in, they have substantially changed the profile of this drug. AVADO and RIBBON1 have not verified the clinical benefit shown in E2100, and considering all the evidence, I cannot conclude that Avastin has been shown to be safe and effective for the metastatic breast cancer indication" (Decision of the Commissioner 2011). Genetech exercised their legal right to request a hearing, but the FDA's Oncologic Drugs Advisory Committee (ODAC) still voted to remove the breast-cancer indication for Avastin. In a Letter to the Editor in the *New England Journal of Medicine*, a member of the committee stated that he made his decision because he did not want to hurt patients with a drug that does not work well or to provide patients with false hope. He imagines how a hypothetical conversation would go with a breast-cancer patient if Avastin was approved to treat metastatic breast cancer: "'Well, I can offer you a drug that will not make you live longer, won't make you feel better, and may have life-threatening side effects, but it will keep your cancer from worsening by an average of 1 to 2 months.' Hope? Or false hope?" (Sekeres 2011).

Avastin: Evaluation of Risks vs. Benefits

Similar to their rational behind the recall of Vioxx, the FDA revoked Avastin's accelerated approval because they believed that the risks were not worth the benefits. The AVADO and RIBBON1 trials failed to confirm the clinical benefit of progression free survival for 5.5 months that was found in the first E2100 trial. Although Genetech argued that the FDA

placed too much emphasis on the progression free survival marker and not enough on other markers, such as hazard ratios, which were found to be in a similar range to the E2100 trial, the FDA stood by its decision. The FDA concluded that the low progression free survival times indicate that Avastin is not worth the risk to patients. However, some patients have made the argument that despite Avastin's effect on most patients, it has worked wonders for a certain group of "super-responders" (Decision of the Commissioner 2011). They argue that the FDA should leave Avastin on the market so that individual patients and their physicians can try the treatment and determine if it is right for them. Furthermore, although Avastin will remain on the market as a treatment for other types of cancers, so doctors can use it off-label for breast cancer, insurers might no longer pay for the drug (Pollack 2011). Costing about $88,000 a year, many women would no longer be able to afford it (Pollack 2011). Metastatic breast cancer is a death sentence for many women. Similar to those with HIV/AIDS, the risk vs. benefit calculation becomes very different in the face of a life-threatening disease. Patients with metastatic breast cancer are willing to take great risks if there is a possibility of prolonging their life, even for a few months time. They are willing to take the risk because there is a chance that they could be one the small group of "super-responders". For a patient facing imminent death, any chance may be worth taking.

Final Judgment on the Avastin Decision

The FDA certainly had a difficult decision to make in the case of Avastin. While individual anecdotes are moving, they offer the FDA no concrete evidence, which the FDA needs to base its decision on. Additionally, "the precedent that [would] be established if the FDA [reversed] its decision on withdrawing [Avastin's] labeling for metastatic breast cancer not because of changing scientific evidence, but in response to philosophical and political

counterarguments" would hinder the agency's credibility (Carpenter 2011). However, credibility is a small price to pay when patients' lives are at stake. In *The New York Times*, Dr. Yashar Hirshaut, an oncologist in Manhattan, criticized the FDA for their stringent reliance on evidence, despite the fact that patients are suffering from a life-threatening disease and already have limited options: "Of course we want everything to be evidence-based. I also like the American flag and apple pie. You say, 'This person is dying right here and I need something that will help, and there's a logical construct that I can see how it will help.' " (Kolata 2008). While Avastin was not shown to be as effective as was originally thought, the small possibility of prolonging life, even by just a month, may be worth the risk for many persons suffering from metastatic breast cancer. However, by failing to extend Avastin to regular approval, the FDA prevents the majority of patients from accessing the drug because insurance companies no longer have to cover it. The FDA should not have revoked Avastin's accelerated approval because it is a drug for the terminally ill. Patients diagnosed with metastatic breast cancer have few other effective options and are likely to die from their cancer. Prolongation of life is invaluable to these patients and their family members. The FDA must take the nature of the disease into greater account when making their decisions. The agency should use a different standard of review when the drug being assessed is for terminally ill patients with few or no other options.

Expedited Approval and Informed Consent

The FDA should continue to use expedited approval, provided that patients are made clearly aware of the difference between research and treatment. Evaluations of the streamlined approval process demonstrate that it is both economically and socially beneficial. A *2010 Project FDA Report* analyzed the use of streamlined approval for three drugs: HAART, for HIV/AIDS; Rituxan, for non-Hodgkin's lymphoma; and Herceptin, for breast cancer. One significant social

advantage that the research found was that the early sale of these drugs, due to the streamlined approval process, benefited patients far more than it benefited the pharmaceutical firms that developed them. For example, Herceptin was worth $137 billion to patients with breast cancer, but only $9 billion in profits for the firm (Philipson 2010). Additionally, a developmental process that allowed Herceptin to enter the market one year earlier would have increased the benefit to patients by $8 billion, a 6% increase (Philipsion 2010). Researchers calculated these economic values by using a "willingness to pay" (WTP) model. WTP is influenced by a patient's income, the year in which the disease began and the survival benefits conferred by the drug (Philipson 2010). It is used to calculate the gross value to the patient of the access to the drug in any particular year, and then the net benefit is determined by subtracting the cost of drug itself (Philipson 2010). The streamlined approval process is beneficial to patients and therefore should be utilized, especially for terminally ill patients.

However, if patients are not clearly informed about the fact that they are receiving an experimental drug for the purpose of research and not a guaranteed treatment, the expedited approval process and clinical trial research itself becomes unethical. Dr. Passamani, who argues that clinical trial research is the most effective and ethical way to evaluate and overcome incomplete information about a treatment, also realizes that "physicians and their patients must be clear about the vast gulf separating promising and proved therapies" (Passamani 1991). If patients are led to believe they are receiving a proven treatment, the trial consequently becomes unethical. For terminally ill patients, who have no other treatment options except to enroll in a clinical trial, this distinction becomes even more crucial. Being a research subject is not the same as being a patient receiving treatment. While the experimental drug might work, there is also the chance that it may not. The most effective way to guarantee that patients are clearly informed is

through a comprehensive informed consent process. Under current FDA regulations, "no investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative" (21CFR50 2012). Informed consent is an important and necessary part of the clinical trial research process because human subjects are donating their time and bodies for the sake of medical knowledge.

An article in the *New England Journal of Medicine* suggests a counter argument, that the obligation to obtain specific informed consent for research should not be absolute, but should "depend on the risk–benefit ratios of the intervention and the alternatives, as well as the degree to which the patient would be expected to have preferences about the various options for diagnosis or treatment that are under investigation" (Truog 1999) The article argues that in certain circumstances a general agreement to participate in research should be used in place of the stringent protocol for informed consent outlined by FDA regulations because the requirement to obtain informed consent in all clinical research trials is an unnecessary roadblock that prevents the easy evaluation of new forms of technology and new interventions (Truog 1999). This argument is flawed because a therapeutic misconception of clinical research exists in our society. Coined by Paul Appelbaum in 1982, the phrase 'therapeutic misconception' describes patients' "failure to appreciate the difference between research and treatment" (. Many patients wrongly believe that they will be receiving treatment when they agree to participate in a trial, but this is not the case. In many cases, they may just be receiving a placebo, or the experimental drug could harm them more than help them. There are risks associated with any treatment, even those that have been proven safe and effective. However, I argue that patients need and deserve a

comprehensive informed consent process in order to help them properly understand and evaluate the risks of participating in medical research.

Conclusion

The case studies of Vioxx and Avastin highlight several of the ethical and practical issues of the drug approval process, including the nature of clinical trial research, the risk-benefit analysis of new treatments, Contract Research Organizations (CROs) and the ethics of post-marketing research. However, they also reveal the fact that no drug approval process is perfect. Regulations guiding the drug approval process are subject to historical context, public opinion and special interests, just like any government policy. They can and do change overtime, but they will always be criticized by any given subset of the population. Additionally, drugs react differently depending upon the environmental factors that the person is experiencing and the internal conditions that vary from person to person. Regardless of what the FDA decides, it will never please everyone. However, I advocate that the FDA should take a patient centered approach to the drug approval process. First, the FDA should continue to use accelerated approval and work to streamline the approval process further, since it has been shown to benefit patients greatly. Second, the agency should continue to utilize the comprehensive informed consent process. If in the future they can eliminate the therapeutic misconception about research, by better educating patients about the difference between research and treatment, only then would I advocate for streamlining or removing the informed consent process. Until then, patients need to be made fully aware of their role as a research subject. Although the FDA will always be blamed and criticized, if they use streamlined approval and informed consent, at least they will have the patients' best interest at heart.

Bibliography

Anderson, M., Manganiello, M. (2011) Back to basics: HIV/AIDS advocacy as a model for catalyzing change. *Faster Cures, HCM Strategists.*

Brooks, Kristin. (2011, April 29) CRO Industry Update: Leveraging Expertise for Innovation. *Contract Pharma.* Retrieved from http://www.contractpharma.com/issues/2011-05/view_features/cro-industry-update-2011-04-29-10-53-51/

Carpenter, D., Joffe, S., Kesselheim, A. (2011, June 27) Reputation and Precedent in the Bevacizumab Decision. *New England Journal of Medicine.* Retrieved from nejm.org.

Decision of the Commissioner - Proposal to Withdraw Approval for the Breast Cancer Indication of Avastin (Bevacizumab). (2011, Nov. 18) *Department of Health and Human Services: Food and Drug Administration.* Docket No. FDA-2010-N-0621.

Eisenburg, Rebecca A. (2005, March 31) Learning the value of drugs – Is rofecoxib a regulatory success story? *New England Journal of Medicine*. 352:13. Retrieved from nejm.org.

Greenburg, Michael. AIDS, Experimental Drug Approval, and the FDA New Drug Screening Process. *Journal of Legislation and Public Policy*. 3:295. Retrieved from http://128.122.51.12/ecm_dlv2/groups/public/@nyu_law_website_journals_journal_of_legislation_and_public_policy/documents/documents/ecm_pro_060626.pdf

Greener, M. (2008, March 9) First do no harm: Improving drug safety through legislation and independent research. *European Molecular Biology Organization.* U.S. National Library of Medicine. National Institutes of Health. Retrieved from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2267386/

Growth in the Breast Cancer Drug Market Through 2021 Will Be Driven by New Entrants from Roche/Genentech and Novartis in Select Market Segments and an Increase in Incident Cases. (2012, August 16) *Business Wire*. Retrieved from http://www.businesswire.com/news/home/20120816005718/en/Growth-Breast-Cancer-Drug-Market-2021-Driven

Henderson, Gail. (2007, November) Clinical Trials and Medical Care: Defining the Therapeutic Misconception. *PLoS Medicine*. 4.11. Retrieved from http://www.genome.duke.edu/seminars/journalclub/documents/Therapeutic%20Misconception.pdf

Herper, M., Langreth, R. (2009, June 22) Trouble for Roche's Avastin? *Forbes Magazine*. Retrieved from http://www.forbes.com/forbes/2009/0622/cancer-drugs-oncology-trouble-for-roche-avastin.html

Kolata, G., Pollack, A. (2008, July 6) Costly Cancer Drug Offers Hope, but Also a Dilemma. *The New York Times*. Retrieved from http://www.nytimes.com/2008/07/06/health/06avastin.html?pagewanted=all&_r=0

Mello, M., Goodman, S., Faden, R. (2012, Sept. 6) Ethical Considerations in Studying Drug Safety — The Institute of Medicine Report. Health Law, Ethics and Human Rights. *New England Journal of Medicine.* 367:10. Retrieved from nejm.org.

Morrow, D. (1999, August 3) The Markets: Market Place; Pushing new arthritis drugs, Monsanto and Merck step up sales calls to doctors. *The New York Times.* http://www.nytimes.com/1999/08/03/business/markets-market-place-pushing-new-arthritis-drugs-monsanto-merck-step-up-sales.html

Oberholzer-Gee, F., Inamdar, S. (2004, Nov. 18) Merck's Recall of Rofecoxib — A Strategic Perspective. *New England Journal of Medicine*. 351:21. Retrieved from nejm.org.

Passamani, Eugene. (1991, May 30) Clinical trials – are they ethical? *New England Journal of Medicine.* 324:22. Retrieved from nejm.org.

Pharma and Biotech Industry Global Report -2011 (2011). *IMAP Inc.*

Philipson, T., Sun, E. (June 2010) Cost of Caution: The Impact on Patients of Delayed Drug Approvals. Project FDA Report. Manhattan Institute.

Pollack, A. (2011, November 18) F.D.A revokes approval of Avastin for use as breast cancer drug. *The New York Times.* Retrieved from http://www.nytimes.com/2011/11/19/business/fda-revokes-approval-of-avastin-as-breast-cancer-drug.html?ref=avastindrug

Presley, Holly. Vioxx and the Merck team effort. *The Kenan Institute for Ethics at Duke University.* Retrieved from dukeethics.org.

Promoting Safe and Effective Drugs for 100 Years (2006) *FDA Consumer Magazine – The Centennial Edition.* FDA: U.S. Department of Human Services. Retrieved from http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/PromotingSafeandEffectiveDrugsfor100Years/default.htm

Sekeres, M. (2011, October 13) The Avastin Story. *New England Journal of Medicine.* 365:15. Retrieved from nejm.org.

Shuchman, Miriam. (2007, Oct. 4) Commercializing clinical trials - risks and benefits of the CRO boom. *New England Journal of Medicine.* 357:14. Retrieved from nejm.org.

Truog R., Robinson, W., Randolph A. (1999, March 11) Is Informed Consent Always Necessary for Randomized, Controlled Trials? New England Journal of Medicine. 340:10. Retrieved from nejm.org.

Vioxx and Other Painkillers: More Confusion, Less Relief? (2005, March 30). Law and Public Policy: Knowledge@Wharton. *University of Pennsylvania.* Retrieved from http://knowledge.wharton.upenn.edu/article.cfm?articleid=1151

Wood, Alastair. (2008, April 24) Playing Kick the FDA – Risk Free to Players but Hazardous for Public Health. *New England Journal of Medicine*. 358:17. Retrieved from nejm.org.

Walsh, R. (2010, Oct. 29) A history of: Contract Research Organisations (CROs). *Pharmaphorum*. Retrieved from http://www.pharmaphorum.com/2010/10/29/a-history-of-contract-research-organisations-cros/

21CFR50 (2012, April 1) Code of Federal Regulations. Title 21- Food and Drugs, Chapter 1- Food and Drug Administration, Department of Health and Human Services. Subchapter A-General, Part 50 Protection of Human Subjects. Retrieved from http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=50&showFR=1&subpartNode=21:1.0.1.1.19.2