Troglitazone: An Analysis of Warner-Lambert's Utilitarian Approach

STS Research Paper
Presented to the Faculty of the
School of Engineering and Applied Science
University of Virginia

By

Sarah Glatz

May 14, 2021

On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

Signed: _____

Approved: _____ Date _____
Benjamin J. Laugelli, Assistant Professor, Department of Engineering and Society

Introduction

Troglitazone, a novel antidiabetic drug that was approved and marketed in the US under the name Rezulin, was withdrawn after three years on the market due to 99 cases of reported liver failure, leading to 11 liver transplants and 66 deaths. These represent only the cases reported to the Food and Drug Administration (FDA), and some experts believe these numbers to be as low as 10% of the actual affected population (Gale, 2006). This case is often cited as a pharmaceutical tragedy, with the FDA's speedy approval criticized for failing to keep the drug off the market.

While scholars have analyzed the various actors such as doctors, the FDA, patients, public interest groups, the media, and manufacturer Warner-Lambert and its role in keeping troglitazone on the market, there has been no analysis of Warner-Lambert's utilitarian approach in keeping troglitazone on the market despite the warning signs of adverse effects caused by the company's product. Without this perspective, we fail to fully understand what motivations and calculations enabled Warner-Lambert to continue selling troglitazone.

In applying a utilitarian framework, I seek to identify the ethical calculations that Warner-Lambert used to justify its actions by analyzing the intensity, certainty, and number of people to which the consequences of its product extended. Through the analyses of clinical trial data submitted to the FDA by Warner-Lambert along with subsequent reviews by the FDA, I will validate the claim that Warner-Lambert's utilitarian approach attempted to place objective value on individual human lives in order to maximize financial gains and bring a novel therapy to market.

Background

Type II diabetes is a chronic disease characterized by the body's insensitivity to insulin. Cells are unable to uptake glucose, resulting in high glucose levels in the bloodstream, which can be fatal if left untreated. At the time of troglitazone's approval in 1997, the Centers for Disease Control and Prevention (CDC) estimated that 10.11 million people in the US had diabetes, 90-95% percent of whom had type II (CDC, 2017). Though there were existing therapies, troglitazone was the first in a novel class of drugs, meaning that its mechanism of action was completely unprecedented. While this fact led to media hype around the drug, it also meant that there could be side effects that had never been seen before due to its novelty. One of these side effects was hepatotoxicity, liver damage or failure (Parker, 2002).

When troglitazone was approved by FDA by 1997, the media and scholars questioned the quickness of its approval. Clinical trials only require new products to show efficacy in relation to placebo. In the clinical trials, 2% were found to have elevated liver enzymes, meaning that they suffered liver damage during their use of the drug (Gale, 2006). There was no clear reason as to why this was happening or which population it would happen to. While Warner-Lambert did report these findings and listed them in the warnings in the product label, the company did not find them concerning enough to keep the drug from coming available to the public.

Once troglitazone was approved, more reports of liver toxicity were reported to the FDA in post-marketing monitoring. Warner-Lambert tried to account for this by sending out warning letters to physicians in "Dear Healthcare Provider" letters, telling physicians to not be too concerned and re-emphasize the safety warnings in the labelling. The FDA suggested that physicians conduct monthly liver enzyme monitoring after prescribing drug to mitigate risk, but subsequent analysis showed that this practice was unrealistic and not carried out effectively (Graham, 2001).

Meanwhile in the UK, troglitazone was removed from the market just 6 weeks after its launch, with the UK Medicines Control Agency stating "the risks of troglitazone therapy outweigh the potential benefits (Gale, 2001)." It remained on the US market for another 2 years and 3 months following the withdraw in the UK (Gale, 2006). Warner-Lambert insisted that the approval by the FDA signified its safety and efficacy. With pressure from the advocacy group Public Citizen, who raised concerns about the downplaying of adverse effects to patients in the marketing materials, the FDA forced Warner-Lambert to withdraw troglitazone from the market.

Literature Review

While the Rezulin Tragedy is mentioned in various biomedical and clinical ethics papers, the ethicality of Warner-Lambert's actions has not been thoroughly analyzed. In a scholarly review of Tragedies in Clinical Trials, Bansal et al. (2015) refer to the root cause of the "Tragedy of Rezulin" being "approval of drug even after poor clinical safety data," referring to Warner-Lambert's downplaying of laboratory findings showing elevated liver enzymes. In a 2002 New York district court case against Warner-Lambert, biomedical research ethics were brought to the attention of the court by the plaintiff but were dismissed because they were "irrelevant in a case where liability is premised on legal, not ethical, standards, and likely to prejudice and confuse fact-finders concerning the pertinent legal standards" *(In Re Rezulin Products Liability Litigation*, 2002).

Edwin Gale is one scholar who has done significant work in synthesizing the network of actors complicit in the troglitazone approval and subsequent deaths. He argues that the "medical community remained resolutely silent on the subject of patient safety. No prominent physician, anywhere in the world, ever stood up to say that a pill for diabetes is not worth dying for" (Jörgens & Porta, 2020). Gale also brings the FDA's fast-track approval process into question,

along with the role of public interest group Public Citizen in drawing attention to the case, leading to the recall of the drug. In his analysis of Warner-Lambert, Gale argues that the clinical trial data that was submitted to the FDA for marketing approval showed a 2% liver toxicity rate among participants, and that this data could have been extrapolated in 1997 upon its submission, thus avoiding harm to the other 99 patients who suffered liver failure post drug approval by the FDA in the two years and three months that the drug was allowed on the market, with no additional drug safety information (Gale, 2006).

Despite analysis and public attention to the drug post-marketing and the scope of harm that the drug caused to the diabetic community, along with questioning the haste with which the FDA approved the drug, Warner-Lambert's actions have not been formally analyzed as a calculated cost-benefit approach. For this reason, I will examine the documents that Warner-Lambert submitted to the FDA when seeking approval for troglitazone and identify the ways in which Warner-Lambert took a utilitarian approach, valuing and emphasizing certain consequences over others.

Conceptual Framework

To assess the moral calculations that Warner-Lambert's made regarding the testing and approval of troglitazone, this paper will perform an analysis of Warner Lambert's FDA approval submission using the utilitarian ethical framework. Utilitarianism is a form of consequentialism, meaning that net outcomes should be judged for their morality rather than the courses of action taken to achieve the outcomes (Van de Poel and Royyakers, 2011). Jeremy Bentham founded utilitarianism, presenting the utility principle as the moral criterion by which all actions should be judged. According to Bentham's utility principle, a good action is one that leads to the greatest happiness for the greatest number of people. Bentham argued that pleasure resulting

from an action is an indicator of its ethicality, drawing on the value theory of hedonism, that pleasure is the only thing that is good in and of itself. Maximizing pleasure means minimizing pain, and evaluating morality using a utilitarian framework often looks much like a cost-benefit analysis, which I argue is what Warner-Lambert did when determining that losing a certain number of lives was acceptable if the gains could outweigh these losses. In measuring a pain or pleasure, Bentham argued that one must consider its intensity, duration, certainty or uncertainty, propinquity or remoteness, and the number of people to which it extends Van de Poel and Royyakers, 2011). An action that results in pleasure is good, while an action that results in pain is bad.

In applying this framework to Warner-Lambert's decision to release troglitazone to the US market and its delay in withdrawing the drug, I seek to identify the utilitarian factors that justify the consequences of Warner Lambert's decision. I will outline the calculated approach that Warner-Lambert took a when presenting and analyzing the side effects of troglitazone in an attempt to maximize the benefits of troglitazone's approval.

Analysis

Using a utilitarian lens to analyze the costs and benefits of the novel drug troglitazone, one could make the argument that Warner-Lambert's decision to market the drug and continue selling it was ethical. This analysis does not attempt to critique the morality of utilitarianism, but rather seeks to assess the case by applying a utilitarian framework to the benefits yielded by one particular actor, the drug manufacturer Warner-Lambert, in drug development, trials, and marketing, and examine the ways in which the scientists and executives at Warner-Lambert calculated the risks in order to justify the harm troglitazone caused.

Scope of consequences: Troglitazone versus placebo

Warner-Lambert emphasized troglitazone's effectiveness over placebo, which allowed the company to artificially inflate the intensity and scope of positive consequences troglitazone could have. This presentation of data is not uncommon since FDA approval only requires that new pharmaceuticals show efficacy in comparison to no intervention at all rather than in comparison to the current interventions on the market. Two metrics for measuring blood glucose are FSG (fasting serum glucose) and HbA1c (hemoglobin A1c) levels. Given that type II diabetics have reduced insulin sensitivity, their cells are unable to absorb glucose when untreated, resulting in a rise in blood glucose levels. In its submission for FDA approval, Warner-Lambert showed the efficacy of various doses of troglitazone in managing blood glucose

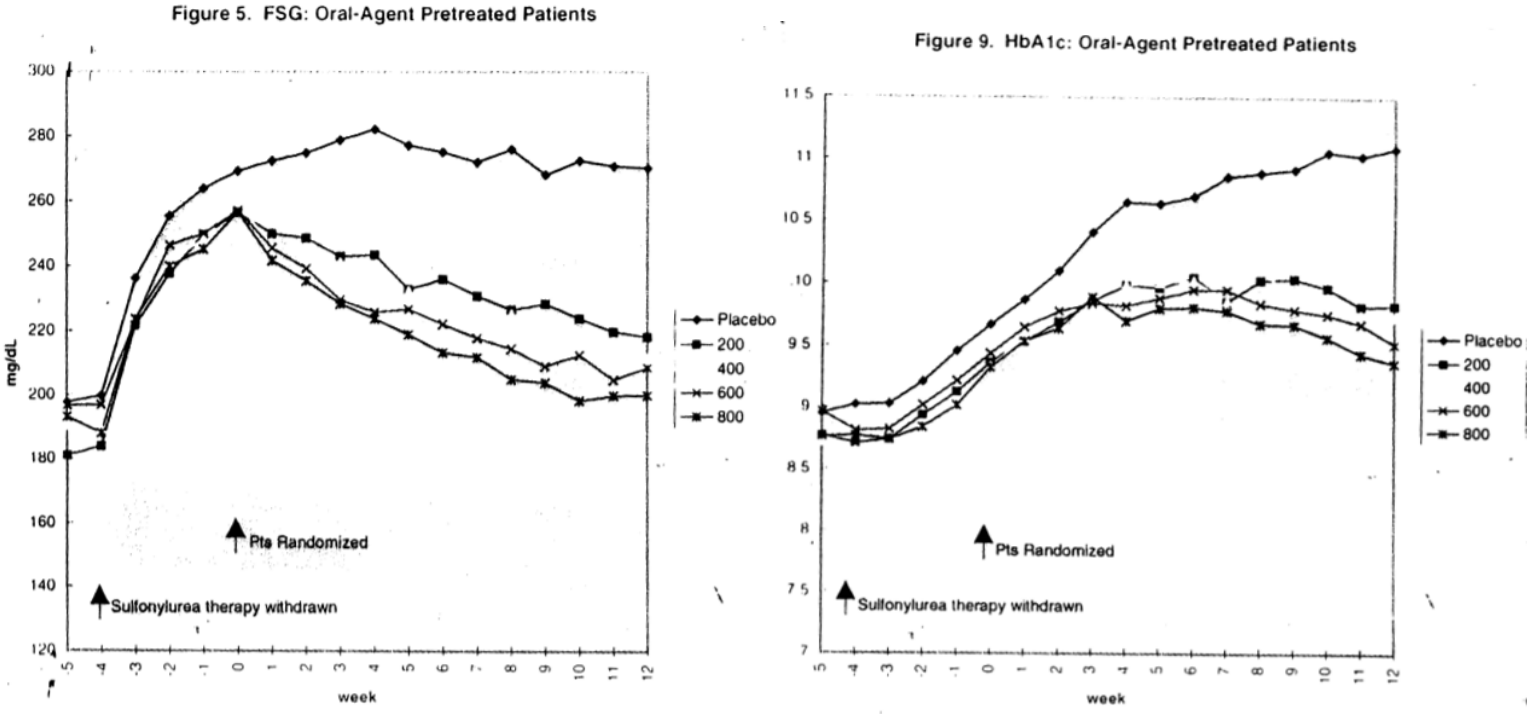

Figure 1. *FSG and HbA1c levels in response to varying doses of trolgitazone compared to placebo* (FDA, 1997)

levels when compared to placebo. In both graphs shown in Figure 1, FSG and HbA1c levels are lower than placebo for all dosages of troglitazone.

In this presentation of the data, troglitazone is clearly effective at managing glucose levels when compared to placebo. From a utilitarian perspective, if we assume that all type II diabetics were untreated, the number of people to which this benefit could extend was large. In 1997, the year of its approval, 10.11 million people in the US alone had diabetes, 90-95% of whom are estimated to have type II (CDC, 2017). Using this data, approximately 9.1 million Americans would benefit from troglitazone. This was a considerable market for Warner-Lambert and was likely a factor that was used to justify bringing the drug to market. A shortfall of this analysis is its failure to account for other existing therapies. Competing and comparably effective drugs make the population in need of the novel therapy troglitazone much smaller. In 1997, there were in fact other antidiabetic drugs available, so a comparative effectiveness analysis of troglitazone with other therapies would be more representative of troglitazone's potential benefits.

Scope of consequences: Troglitazone versus existing therapies

Comparing troglitazone to other therapies allows for a more realistic view of its potential utility by limiting the scope of benefits to those type II diabetics for whom the current therapies do not work. In Warner-Lambert's submission for approval to the FDA, the company included Figure 2. These two graphs show troglitazone monotherapy versus glyburide monotherapy and its effects on baseline FSG and HbA1c after one year. Along the x-axis is first glyburide, the primary antidiabetic drug available at the time, compared with various doses of troglitazone, with the right-most bars depicting the combination of the two treatments. An inverted bar means that the average blood sugar levels decreased over the course of the year, which was the desired

outcome. Troglitazone and glyburide combination therapy did present novel advantage for glucose management, which is depicted by the inverted bar graph. Mean patient HbA1c and FSG levels were lower after a year of treatment, but troglitazone, when used as a monotherapy, did not show any significant benefit when compared to the current therapy.

Viewing these comparative effectiveness results through a utilitarian lens, the intensity of the positive consequences is no better than that of the current therapy. As depicted by the first four bars on each graph, both troglitazone and glyburide managed blood glucose levels to about the same extent. From a utilitarian perspective, one must also consider how the existence of another comparably effective treatment reduces the number of people to which the positive consequences of glyburide can extend. Considering the above results, the benefits of troglitazone are limited to only the small population that did not respond to glyburide instead of the entire 9.1 million Americans with type II diabetes. This fact did not stop Warner-Lambert from seeking approval of troglitazone monotherapy as a direct competitor for glyburide. Even though the data

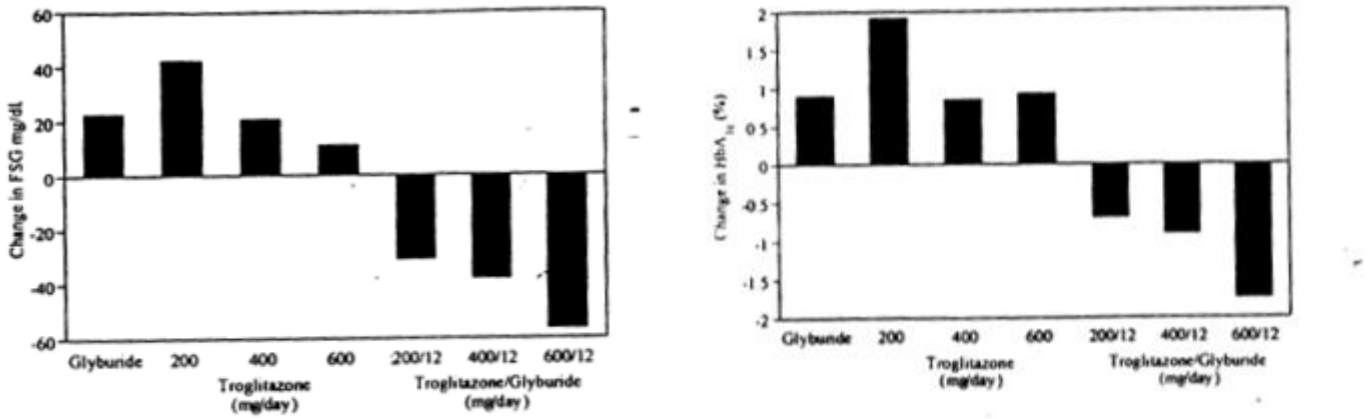

FIGURE 2. Mean Change From Baseline in FSG at Week 52 (ITT) FIGURE 3. Mean Change From Baseline in HbA_{1C} at Week 52 (ITT)

Figure 2. *Comparative effectiveness of troglitazone with existing therapy glyburide* (FDA, 1997)

suggest its utility was no better than the existing therapy, troglitazone was marketed to all type II diabetics, allowing it to reach the scope of harm it did once adverse outcomes became evident. Warner-Lambert's financial interests in seeking to reach the highest number of patients as possible were likely a motivating factor in this decision, which would prove deadly to at least 66 patients.

Scope of consequences: Troglitazone as a monotherapy

Though Figure 2 shows that troglitazone was not any more effective than the current therapy when taken on its own, Warner-Lambert still sought approval for the drug as a monotherapy, which allowed for it to be marketed to all Type II diabetics, thereby increasing the scope of its consequences. Ronald Steigerwalt, a pharmacology reviewer at the FDA, approved the use of troglitazone as a monotherapy in 1997 stating that no new pharmacology data were needed for this use case, and that the initial labeling and carcinogenicity concerns had already been resolved (FDA, 1997). Perhaps Steigerwalt was not aware of just how harmful this approval would prove to be. Warner-Lambert's push for the monotherapy approval, coupled within the unpredictable side effects of troglitazone, subsequently brought about the deaths of 66 patients. As seen in Figure 2, troglitazone did not perform any better than the current glyburide tablets that were on the market at the time. Warner-Lambert presented this information to the FDA, though it is not the FDA's responsibility to determine if a drug is more desirable than the current state of the art, rather that it is just better than placebo. The approval of troglitazone as a monotherapy meant that Warner-Lambert was granted approval to market troglitazone not only as a combination therapy, which was shown the be most effective in Figure 2, but also as an individual therapy to the entire population of type II diabetics.

This push by Warner-Lambert was an attempt to increase the drug's positive consequences by further increasing both the number of people who would take troglitazone and the duration of its benefits by making troglitazone a mainstream competitor with glyburide. Looking solely at the data that presents the benefits of troglitazone as a new therapy for type II diabetics, the number of people which troglitazone can help is limited, but ethical, considering it will offer utility to those who did not respond to glyburide. What this analysis fails to consider is the negative consequences of troglitazone, which were highly uncertain as well as the scope of this harm when marketed to all type II diabetics. Troglitazone led to liver failure in some users and there was no way to predict whom it would harm. Public Citizen, who is credited for bringing national attention to the harm of troglitazone, makes the case that the side effects of troglitazone far outweigh the benefits, especially considering the drug did not perform markedly better than other options ("Patients, doctors not warned of dangers of new diabetes drugs". 2000). This point must be further articulated, and the evidence below suggests the Warner-Lambert downplayed inevitable harm that troglitazone would cause.

Intensity of consequences

The intensity of negative consequences is what led to troglitazone's withdrawal from the market, but the above figures fail to mention the potential for liver failure. Warner-Lambert downplayed the risk of liver failure in the way it tested and presented troglitazone, allowing the company to justify its harm through net utility offered to the greater type II diabetic population. In a review by the FDA, medical reviewer Dr. Robert Misbin addressed the alarming levels of liver failure being reported along with the above data as part of the initial approval submission package. Figure 3 shows a table that was submitted in Warner-Lambert's Investigational New Drug application to the FDA based on information available up to February 1, 1997. The clinical

trial consisted of 2510 patients who were enrolled to take troglitazone for six months. Alanine transaminase (ALT) is an enzyme found in the liver that is responsible for converting protein into energy for the liver cells (*Liver Function Tests - Mayo Clinic*, n.d.). Elevated ALT levels in the bloodstream are an indicator of liver damage. ULN is the upper limit of normal. Summing the "total" column of Figure 3, 4.7% of participants experience elevated ALT. In column three, we see that 62 patients had to be withdrawn from the initial study due to fear of further liver damage. This data alone is cause for concern and questioning of the potential negative consequences of troglitazone.

While this initial reporting did not include any cases of liver failure or death, FDA medical reviewer Dr. Robert Misbin MD raised the question as to whether the data was representative of what would happen to a patient who took the drug for longer for six months as well as what would have happened to those patients had they not been withdrawn. This table being one of the only references to the adverse effects of troglitazone in the approval package, Misbin suggests that the data presented in Figure 3 does not comprehensively represent the adversely affected population. In his review of the submission, Misbin (FDA, 1999) wrote:

> The discussion of patients with elevated ALT levels in the text of the safety update pertained to patients reported as "elevated ALT levels" as the COSTART [Coding Symbols for a Thesaurus of Adverse Reaction Terms] term. Patients were apparently not included in this section if the COSTART term was liver function test abnormal. (p. 18)

Misbin articulates that this data is very likely underrepresenting the number of patients who experienced liver damaged due to the way the data was either excluded or included in the report. As the title of the Figure 3 suggests, this data only represents the patients whose ALT levels were recorded as elevated. If a patient's provider reported his/her liver function test as "abnormal", which could have very well been elevated ALT, it was not added to the data. This means that there were even more patients who suffered adverse liver events, but due to the way they were reported, they were considered insignificant.

NDA Data base
ALT Elevations during Clinical Trials

ALT max	Continued on drug Value at end of trial		Withdrawn	Total
	Normal	Abnormal**		
>3 xULN (102 U.L)	17	8	23	48 (1.9%)
>5xULN (140 U/L)	16	6	20	42 (1.7%)
>8xULN (272 U/L)	5	3	14	22 (0.9%)
>30xULN (1020U/L)	----	---	5*	5* (0.2%)

Data from submission to IND 52828, October 21, 1997
Upper limit of normal taken as 34U/L
N= 2510 (n= 1715, 3 months of longer)

* 2 jaundiced
** normalized following drug withdrawal

Figure 3. *Alanine transaminase elevations reported during clinical trials* (FDA, 1997)

Despite these concerns, Warner-Lambert did not submit further data, which made the risk of liver damage and irreversible harm to the liver seem minimal. Gale (2006) argues that the deaths and liver failure that followed in the next three years could have been extrapolated from the data contained in Figure 3. In assessing the data solely from the clinical trial reporting in accordance with utilitarian principles, intensity of harm and the number of people to which it would extend was minimal given that, at least according to Warner-Lambert's report, no patients suffered liver failure and their condition was reversed once they stopped taking troglitazone. Taking a utilitarian stance, once treatment was ended, the duration of harm was minimal. Though another important element of utilitarian ethics was harder to ensure, the certainty or uncertainty

of injury. Once the drug was approved, the intensity of harm was also much greater than what Warner-Lambert reported, leading to irreversible liver damage and at least 66 deaths.

Uncertainty

One aspect of troglitazone that made it particularly dangerous, is that there was no indicator of who would respond negatively, making it difficult to create measures that would reduce the scope of harm. In an effort to mitigate this risk, the FDA pushed for added precautions and safety monitoring for patients taking troglitazone. Table 1 shows the evolution of FDA recommendations. As the case against troglitazone became clearer, the FDA resisted recalling the drug, deciding to first try and reduce the number of adverse events by suggesting

Study Cohort	Inclusive Dates	Liver Enzyme Monitoring Recommendations	Cohort Size
1	Apr 1, 1997-Oct 27, 1997	None	2307
2	Dec 1, 1997-Jun 30, 1998	Baseline; monthly, 6 times	2823
3	Jul 28, 1998-Jan 26, 1999	Baseline; monthly, 8 times	1673
4	Mar 26, 1999-Sep 24, 1999	After advisory meeting; baseline; monthly, 12 times, from mid June to end of period	800

Table 1. *Evolution of liver monitoring recommendations* (Graham, 2001)

patients have liver enzymes monitored each month for the first six months of use. This then was escalated to eight months and was subsequently increased again to twelve months with an enzyme test every three months following the initial twelve.

Though Warner-Lambert continued to insist that the drug was indeed safe, citing the FDA's approval of it as a credit to its safety, an independent analysis by the United Health Group suggested that liver enzyme testing was not being consistently carried out despite pressure from the FDA. The guidelines did cause for an increase in the number of patients who underwent baseline liver enzyme testing, but as shown in Figure 4, monitoring dropped off over subsequent

months, meaning that the FDA's recommendation for monthly liver enzyme monitoring as a way to reduce number of adverse drug response was likely unsuccessful (Graham, 2001).

From a utilitarian viewpoint, this was an effort to minimize the uncertainty and the number of people who would experience negative consequences of troglitazone. The efforts by the FDA and Warner-Lambert to reassure patients and providers that the product was safe failed. But were these costs justified? Did troglitazone provide enough benefit that the risk of 4.7% of the patients experiencing elevated ALT and potential liver failure was justified? Under utilitarianism, one can justify the negative outcomes if they are offset by greater positive gains. Utilitarianism attempts to place values on different outcomes, and in this case one must justify that the loss of human life and liver failure for a small group of patients is acceptable for the gain of the greater type II diabetic community. While I am not advocating for this approach, this evidence makes clear how these calculations came into play in Warner-Lambert's decision to leave the drug on the market.

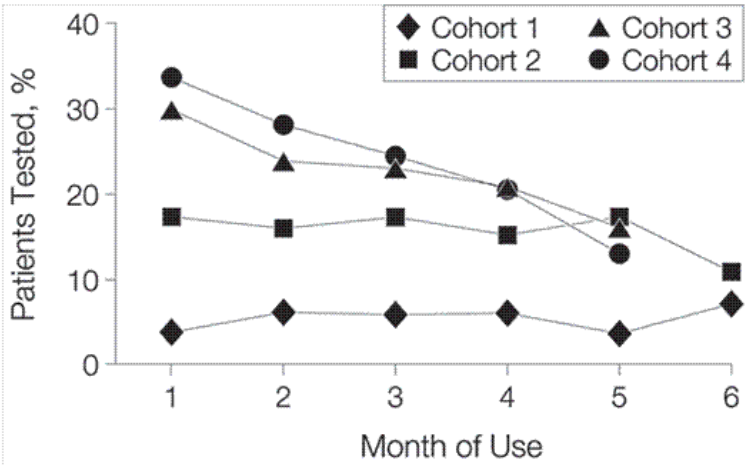

Figure 4. *Liver enzyme monitoring participation per cohort referenced in Table 1* (Graham, 2001)

Conclusion

Warner-Lambert's utilitarian approach to reporting and presenting data ultimately lead to the death of at least 66 patients who were prescribed its product. Warner-Lambert calculated the risks in such a way that allowed them to favorably portray the intensity, duration, uncertainty,

and the number of people to which the consequences troglitazone would extend. In taking this approach, Warner-Lambert sought to frame the consequences in a way that would maximize the benefit to greater diabetic community along with the manufacturer's profitability. Utilitarianism seeks perform a cost benefit-analysis on outcomes resulting from a given action. While this approach is sometimes justified, cases such as that of troglitazone seek to place objective value on human lives.

This analysis presents the calculations that Warner-Lambert made while seeking approval. The case outlined in this paper is not the only instance where a company performed a cost benefit analysis of rewards, ultimately seeking to justify harm through juxtaposition with other benefits. Scholars and business leaders should work to develop an ethical framework that better acknowledges the conflicting rewards inherent to the market model of pharmaceutical innovation. As engineers, we must strive for higher standards to measure success that do not diminish analyses to mere cost-benefit calculations of outcomes, especially when human life is on the line. Biomedical device and pharmaceutical companies must hold themselves to a higher standard than simply clearing the regulatory hurdles. If we aim to use technology and science to improve the lives of others, we must ensure that we are practicing care and not diminishing the value of any one human life in the process.

3886 words

References

Adams, C., & Stern, G. (2000, March 22). Warner-Lambert to remove Rezulin from market following FDA reviews. *Wall Street Journal*. https://www.wsj.com/articles/SB953685909426324358

Bansal, P., Gupta, S., Christopher, A., & Gupta, V. (2015). Tragedies in clinical trials—A history wrapped up. *International Journal of Clinical Pharmacology & Toxicology*, 169–178. https://doi.org/10.19070/2167-910X-1500029

Centers for Disease Control and Prevention. (2017). *Long-term trends in diabetes* https://www.cdc.gov/diabetes/statistics/slides/long_term_trends.pdf

Gale, E. A. (2001). Lessons from the glitazones: A story of drug development. *The Lancet, 357*(9271), 1870–1875. https://doi.org/10.1016/S0140-6736(00)04960-6

Gale, E. A. M. (2006). Troglitazone: The lesson that nobody learned? *Diabetologia*, *49*(1), 1–6. https://doi.org/10.1007/s00125-005-0074-6

Graham, D. J. (2001). Liver enzyme monitoring in patients treated with troglitazone. *JAMA, 286*(7), 831. https://doi.org/10.1001/jama.286.7.831

In re Rezulin products liability litigation, 00 Civ. 2843 LAK, MDL No. 1348 (2002) Retrieved March 5, 2021, from https://casetext.com/case/in-re-rezulin-products-liability-litigation-255

Jörgens, V., & Porta, M. (2020). *Unveiling diabetes—Historical milestones in diabetology*. Karger Medical and Scientific Publishers.

Liver function tests—Mayo Clinic. (n.d.). Retrieved March 10, 2021, from https://www.mayoclinic.org/tests-procedures/liver-function-tests/about/pac-20394595

Parker, J. C. (2002). Troglitazone: The discovery and development of a novel therapy for the treatment of type 2 diabetes mellitus. *Advanced Drug Delivery Reviews*, *54*(9), 1173–1197. https://doi.org/10.1016/S0169-409X(02)00093-5

Patients, doctors not warned of dangers of new diabetes drugs. (2000). Public Citizen. Retrieved March 5, 2021, from https://www.citizen.org/news/patients-doctors-not-warned-of-dangers-of-new-diabetes-drugs/

U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Approval package for Rezulin, August 08, 1997. Retrieved March 5, 2021, from https://www.accessdata.fda.gov/drugsatfda_docs/nda/97/020720_s02_s03_s05ap.pdf

U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Medical reviews of Rezulin, March 16, 1999. Retrieved March 5, 2021, from https://www.accessdata.fda.gov/drugsatfda_docs/nda/99/20720S12S14_Rezulin.cfm

van de Poel, I., & Royakkers, L. (2011). *Ethics, technology, and engineering: An introduction.* Blackwell Publishing