The Downfall of the "Fen-Phen" Weight Loss Drug Combination

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By

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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.

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Introduction:

The term "fen-phen" refers to the combination of two drugs, fenfluramine and phentermine, used for weight loss in the mid-1990s. The Food and Drug Administration (FDA) individually approved both of these drugs as an appetite suppressant to be used in addition to diet and exercise regimens for weight loss. However, neither of these drugs gained a large market share due to the lack of weight loss results experienced by patients (Molitor, B., & Spielberger, K., 2017). In 1992, Dr. Michael Weintraub published results from a double-blind clinical trial of 121 patients who took the fen-phen combination, illustrating promising weight loss results and fewer side effects than taking the drugs alone (M Weintraub et al., 1992). As prescriptions for this drug cocktail began to rise, just two years later, an echocardiography technician at MeritCare saw links between this diet drug combination and valvular heart disease (VHD) (Schiller, N. B., 1999). In January of 1997, a cardiologist at MeritCare contacted the Mayo Clinic, and they worked together to publish these findings in the *New England Journal of Medicine* later that year. Following this, the FDA requested fenfluramine and dexfenfluramine (a purified version of fenfluramine, otherwise known as "Redux") be withdrawn from the market. Six million Americans had taken one of these drugs at this point (Schiller, N. B., 1999). Thousands of lawsuits (individual and class action lawsuits) were filed against American Home Products Inc. (now named Wyeth Pharmaceuticals), the manufacturer of fenfluramine (the diet drug Pondimin). These lawsuits were aimed at plaintiffs receiving compensation and medical monitoring due to the cardiovascular injuries caused by this drug combination (Schiller, N. B., 1999). In August 2000, the court approved a $4.75 billion settlement, which is now valued at $7.65 billion (Levin Sedran & Berman LLP, n.d.).

Most scholarly analyses about the "fen-phen" case discuss the misuse of "off-label" fenfluramine and phentermine prescriptions, the failure of Wyeth to warn the users about the health risks of fen-phen, and Wyeth's failure to withdraw the drug from the market after discovering the adverse events caused by this drug combination (Nutt, P. C., & Wilson, D. C., 2010). The pharmaceutical company, Wyeth, has been found liable to provide compensation in many court cases (Levin Sedran & Berman LLP, n.d.). However, such analyses ignore how Wyeth Pharmaceuticals acted unethically as a drug manufacturer, specifically neglecting their role of care in the manufacturer's relationship with the patient. Recognizing the responsibility of Wyeth Pharmaceuticals in this manner is essential to better understand the dynamics between different actors in the pharmaceutical industry. It is also essential to hold these groups in power to a specific legal and ethical standard to ensure safe practices in these systems. In the following analysis, I will draw on Joan Tronto's care ethics, which breaks down the definition of care into four categories: attentiveness, responsibility, competence, and responsiveness (Sander-Staudt, M., n.d.). I will explain how Wyeth Pharmaceuticals neglected to meet the first three categories and, therefore, acted unethically in the fen-phen case. To support my analysis, I will draw on medical journals, legal documents, and books that provide insight into internal correspondence at Wyeth Pharmaceuticals.

Background:

Fenfluramine and phentermine are appetite suppressants that act in different ways. Fenfluramine is a serotonergic agent (triggers the release of serotonin), and phentermine is an amphetamine-like central stimulant that releases norepinephrine. These drugs lead to feelings of fullness (Schiller, N. B., 1999). However, fenfluramine causes lethargy and depression, while phentermine causes jitteriness. It was believed that the combination of these drugs would

essentially cancel out their respective side effects (Molitor, B., & Spielberger, K., 2017). These drugs both increase serotonin through different mechanisms. Doctors noticed that cardiac valvulopathies in otherwise healthy patients who took this diet cocktail had similarities to serotonin overdose from other medications or from carcinoid syndrome, which is a serotonin-producing tumor of the GI tract (O'Donnell, J., 1998).

Literature Review:

While there is a plethora of evidence of legal discourse with Wyeth Pharmaceuticals in class action suits and individual lawsuits following repercussions from the fen-phen diet drug combination, there is a lack of analysis of whether the company acted unethically. John T. Evans and Robert L. Kerner discuss potential arguments for plaintiffs to use against the manufacturer or the physicians in a court of law. They point out how one could argue that the manufacturer acted unlawfully if they had knowledge about the danger of the fen-phen drug combination, while the physicians had none (Evans, J. T., & Kerner, R. L. Jr., 1998). However, the learned intermediary doctrine could be used by the manufacturer, which explains that they have "fulfilled [their] duty of care when [they] provide all of the necessary information to a 'learned intermediary' who interacts with the consumer of a product" (Evans, J. T., & Kerner, R. L. Jr., 1998) (Volk, D. G., 2016). The learned intermediary would be physicians in this case. The authors additionally point to the role of the physicians, stating how they could be sued for not adequately warning patients about risks associated with the drug combination or for incorrectly prescribing the drug (for cosmetic weight loss instead of for addressing obesity). Although, the physician could then argue that they were not aware of the risks associated with cardiac valvulopathy before the article published in 1997 in the *New England Journal of Medicine* linking the diet drugs to valvular heart disease (Evans, J. T., & Kerner, R. L. Jr., 1998). The authors address the complexity of the

case and highlight how the responsibility for the outcomes of the "fen-phen" drug combination can be attributed to different actors. However, the authors solely address the situation from a legal and liability perspective rather than focusing on the case from an ethical standpoint and whether or not these actors acted in an unethical manner.

In the "Handbook of Decision Making," Paul C. Nutt does discuss how Wyeth Pharmaceuticals acted incorrectly in the "fen-phen" case, attributing these actions to a "'profit driven principle' posture or from an unwillingness to confront an out of control situation." Nutt writes about how Wyeth resisted adding warning labels after reports in 1995 from European investigators pointed out fen-phen causing VHD and primary pulmonary hypertension (PPH). He also writes about how Wyeth intentionally was slow to report data about the health problems being caused by fen-phen. Nutt also attributes their failure to add the warning labels and warn physicians about these issues to concerns about affecting profits (Nutt, P. C., & Wilson, D. C., 2010). While Nutt does a better job of looking at Wyeth's role in this case, he fails to conduct an ethical analysis of the company's actions. Insight into the ethical role of drug manufacturers and pharmaceutical companies is essential for maintaining a safe and transparent consumer environment. Ethical accountability is crucial in an industry with direct health implications for society.

Conceptual Framework:

My analysis draws on Carol Gilligan's and Joan Tronto's theories of care ethics, which allows me to explain how the corporation of Wyeth Pharmaceuticals acted unethically in how they handled the fen-phen weight loss drug case. This theory emphasizes the importance of relationships and discusses how people learn norms and values within contexts with different people instead of just being taught moral principles (van de Poel, I., & Royakkers, L. 2011).

Gilligan emphasizes the importance of mutual responsibility and care for one another, considering how one's abilities or limitations can impact one's ability to make moral decisions (van de Poel, I., & Royakkers, L., 2011). This is especially important if a relationship is "asymmetrical," as a different level of care is warranted based on the specific context and the power dynamic between those in the relationship (van de Poel, I., & Royakkers, L., 2011). Since care ethics discusses different levels of responsibility depending on the relationship's dynamic, this can be applied to the responsibility of the care of a corporation to the consumer, a teacher to a student, or a parent to a child, to give some examples. Other scholars of care ethics, Joan Tronto and Bernice Fischer, define care as "species of activity that includes everything we do to maintain, contain, and repair our 'world' so that we can live in it as well as possible" (Sander-Staudt, M., n.d.). In defining care, Tronto uses four elements to outline this ethical framework: attentiveness, responsibility, competence, and responsiveness (Sander-Staudt, M., n.d.). Attentiveness refers to being aware of someone in need of care, while responsibility refers to being willing to respond to the realization that one is in need. In addition to recognizing when care is necessary, competence is the ability to provide necessary and good care, and responsiveness is the ability to receive the care well (Sander-Staudt, M., n.d.). In the analysis that follows, I will use Tronto's definition of care to evaluate how Wyeth Pharmaceuticals acted unethically in the manufacturing of fenfluramine and dexfenfluramine and in their response to concerns about the "fen-phen" drug combination increasing the risk of PPH and heart valve problems. I will divide the analysis into three elements of care, attentiveness, responsibility, and competence, to illustrate how Wyeth Pharmaceuticals failed to meet the care criteria and, therefore, acted unethically through their actions.

Analysis:

Attentiveness

In evaluating whether Wyeth Pharmaceuticals acted unethically in their role in the "fen-phen" case, I will first show how the company failed to demonstrate "attentiveness" towards the patients taking the fen-phen drug combination- thereby failing to meet the first criteria of ethical care Joan Tronto's theory of care ethics. After reports of cardiac valvulopathy in otherwise healthy, young patients, the article in the *New England Journal of Medicine* cited that:

> "Fenfluramine alters serotonin metabolism in the brain. Phentermine interferes with the pulmonary clearance of serotonin, which may explain its association with primary pulmonary hypertension. Although serotonin levels were not measured in our patients, we postulate that the combination of fenfluramine and phentermine may potentiate the effect or concentration of circulating serotonin and result in valvular injury similar to that seen in patients with carcinoid syndrome or in those taking ergot preparations" (Connolly, H. et al., 1997).

While in a later briefing, Wyeth Pharmaceuticals stated that "the addition of phentermine to Pondimin ['fen/phen'] is *not* an approved use of Pondomin" in a Dear Doctor letter in 1997, it is highly implausible that they were not a proponent of using this combination (Mundy, 2001). Following Weintraub's study showing the improved tolerability of the fen-phen drug combination, the "prescription for phentermine and fenfluramine increased 442% and 6,390%, respectively, from 1992 to 1996" (Goodrick, 2007). Given the dramatic increase of sales in both of the diet drugs, it is clear that the success of each of them was dependent on the other. While Wyeth finally made a statement about how the combined use is "*not* approved," this came after

over four years of skyrocketing sales, so it is reasonable to assume that Wyeth was completely aware of these drugs being used in combination with one another, following the study published in 1992. Further, given that both of these drugs increase the level of serotonin in the body and that there was only a small, short-term study conducted looking at the combination of the two drugs, it seems highly irresponsible for Wyeth not to conduct an investigation on the effects of the drug combination on the body. As a drug manufacturer, Wyeth should have been attentive to the needs of the patients that they would be treating and be proactive to determine if the combination of these drugs would lead to serious adverse events rather than addressing them after the fact. There are serious conditions like "carcinoid syndrome" that are due in part to an excess of circulating serotonin in the body. Given that fenfluramine and phentermine both lead to an increase of serotonin, it seems fairly obvious that a drug manufacturing company with the highest degree of understanding of their drug's mechanism of action would investigate these potential effects.

As I have argued, Wyeth Pharmaceuticals failed to be attentive to the needs of their patients and were complacent in the investigation of the safety of this popular drug combination that brought them large profits. Yet, some believe that the organization with the greatest responsibility in the pharmaceutical industry is the FDA. The responsibility that the FDA holds in the drug regulation process is technically one that supersedes that of the drug manufacturer, at least in the approval process. In a document from the Congressional Research Service, the responsibility is clearly laid out:

> "FDA divides [the] responsibility into two phases. In the preapproval (premarket) phase, FDA reviews manufacturers' applications to market drugs in the United States; a drug may not be sold unless it has FDA approval. Once a drug is on the market, FDA

continues its oversight of drug safety and effectiveness. That postapproval (postmarket) phase lasts as long as the drug is on the market" (Sheikh, 2018).

Since the FDA is the final approver of drugs before they are allowed to be sold to consumers, it could be argued that they have the primary responsibility to ensure the safety of the drugs and to know about any potential adverse effects that could harm the patient. The FDA has responsibilities for "premarket" and "postmarket" approval, meaning that they are responsible for the drug for its entire lifespan and can deny the drug before approval or remove the drug from the market if serious adverse effects arise.

However, in the Pennsylvania Supreme Court court case *Lance v Wyeth,* the family of Catherine Ruth Lance went to court after she died from PPH in 2004 after only taking fen-phen for several months in 1997. The decision of the appeal of the case notes that "primary responsibility for drug safety rests with the manufacturer, which has 'superior access' to information about [its] drugs; especially in the postmarketing phase as new risks emerge" (Saylor, T. G., 2014). While the FDA does have the final approval on if a drug will make it onto the market, the drug manufacturer has the "superior access" to information about how the drug works, its side effects, and who should or should not use it. So, Wyeth Pharmaceuticals was inattentive by not being proactive about determining the dangerous side effects of their drugs and thus acted unethically according to the care ethics framework.

Responsibility

While Wyeth Pharmaceuticals did not take steps to uncover information about their products that could have harmful effects on patients, they also actively did not acknowledge evidence about these harmful effects when presented to them. The International Primary Pulmonary Hypertension Study (IPPHS) came out in 1995 and linked the weight loss drugs

fen-phen and Redux to an increased risk of PPH (Hanlon, 2017). Following refund requests for the drugs after the release of this study, a Wyeth administrator named Kay Anderson sent a memo to Patty Acri in October 1966 saying, “do I need to look forward to spending my waning years writing checks to fat people worried about a silly lung problem?” (Mundy, 2001). The lung problem that Kay Anderson is referring to is PPH, which is a chronic disease characterized by the constriction of blood vessels in the lungs, leading to pressure rising about normal levels (Sather, R., Wojcik, S., & Kang, S., 2025). There is currently no treatment for this disease, and it can be life threatening, as it can lead to heart failure (Mayo Clinic, 2023). In order to constitute “care,” one must be responsible for addressing the needs of those in a relationship once they are made aware of the care needed. Given that the drug manufacturer has proprietary information about the drug, it cannot be expected that the patients would have to fully assess the risks of the drug that they are prescribed. This presents an asymmetrical relationship, a specific type of relationship described in the care ethics framework (van de Poel, I., & Royakkers, L., 2011). While Wyeth was aware of the risk of PPH from the fen-phen drug combination, the IPPHS study further brought to light more information about the potential link between the two (Mundy, 2011). Referring to PPH as a “silly lung problem” means that either Wyeth employees were unaware of the severity of this chronic condition or that they were aware and still thought of it as “silly.” Both speak to the lack of responsibility with key information about their drugs and to the attitude of the employees at Wyeth. Additionally, referring to the patients as “fat people” is unprofessional and reflects a failure to recognize them as patients deserving of care. While drug manufacturers and doctors play very different roles in the pharmaceutical industry, these companies have a duty of care to those who could take their drugs. The sentiment of this memo speaks volumes about how Wyeth participated in this asymmetrical relationship.

The FDA wanted to require a black box warning in response to heart and lung complication risks (Nutt, P. C., & Wilson, D. C., 2010). A memo dated November 21, 1995, from Carrie Smith Cox, Wyeth's VP for Women's Health, further highlights how Wyeth Pharmaceuticals neglects patient care in regard to the risk of PPH:

> "If… Redux has a black box for PPH… this would likely be an extremely strong negative. [The black box] is probably the biggest single factor remaining to determine future sales…The efficacy of Redux is not impressive, and is insufficient for the needs of the patients the doctors would like to prescribe it for…The fact that patients regain weight upon discontinuation is a fairly strong negative" (Mundy, 2011).

A black box is a label that the FDA can require a pharmaceutical company to add to their product's labeling when "serious adverse reactions or special problems occur, particularly those that may lead to death or serious injury" (Murphy, S., & Roberts, R., 2006). A black box warning is the most serious warning that can be assigned to an approved drug label by the FDA (Delong, C., & Preuss, C. V., 2023). While Wyeth was aware of the risks associated with PPH, including the IPPHS study and the reasoning behind the black box, their priorities remained clear: profits from the drugs outweighed the safety responsibility to the patients. The language of "extremely strong negative," followed by referencing "future sales," instead of addressing the actual reasons behind the threat of a black box warning, highlights the sentiment at Wyeth Pharmaceuticals. Wyeth's data only shows a 3% weight loss difference between patients who took fen-phen and placebo (those who did not take the drug but only practiced lifestyle changes) (Elliott, C., 2004). Claiming that the efficacy of Redux is "not impressive" is an understatement, especially given that patients would not even keep the weight off after discontinuing the drug. Wyeth's push against the inclusion of a black-box label after clear risks are presented of a drug where the

benefits are minuscule is irresponsible and neglects the priority of patient safety. The patient is not expected to do their own research to conduct a risk-benefit analysis. Wyeth Pharmaceuticals ignored its corporate responsibility by having access to this information and putting "sales" above patient safety. Thus, they violated the second component of Joan Tronto's definition of care and acted unethically. Based on Joan Tronto's care ethics, for one to care ethically, one must first be attentive and recognize when someone needs care and then be responsible for addressing those needs. The following component of ethical care is "competence," referring to the actual ability and actions of one to provide good care.

Competence

Wyeth Pharmaceuticals failed to be attentive and responsible in responding to the safety concerns about fen-phen, and they also failed the third element of care, competence, by failing to provide care effectively. In response to the pressure of a black box warning due to the accumulating data about the risk of PPH in connection to fen-phen, in January 1997, Wyeth Pharmaceuticals sent a "Dear Doctor" letter to physicians about the Pondimin label changes:

> "PONDIMIN IS AN APPETITE SUPPRESSANT. AND APPETITE SUPPRESSANTS INCREASE THE RISK OF DEVELOPING PRIMARY PULMONARY HYPERTENSION, AN OFTEN FATAL CONDITION" (Mundy, 2011).

The effect of Wyeth Pharmaceuticals including this label on their drug pales in comparison to that of adding a black box warning. The Wyeth marketing team predicted adding a black box warning would lead to a 50% drop in sales (Mundy, 2011). This warning skillfully takes the blame away from the drug they manufactured and instead blames the drug as just being an "appetite suppressant." The use of the ". AND" implies that any appetite suppressant can increase the risk of developing PPH, which is misleading and untrue. The increased risk of PPH

is due to the mechanism of action (MoA) of fenfluramine and Redux and is not a risk that comes with any appetite suppressant. Given that the ordinary person likely knows of other products, substances, or practices that suppress appetite and have not led to PPH, it is fair to assume that a doctor or patient would disregard this labeling as a real risk to be concerned about. However, the reaction to a black box warning would be much more extreme and would lead to a significant decline of prescriptions, as Wyeth predicted sales to be cut in half (Mundy, 2011). Wyeth Pharmaceuticals had failed to be attentive to the needs of their consumers by not recognizing a problem with the drug combination before it harmed people, and they failed to be responsible for their duty of care by putting safety above profits. Finally, Wyeth Pharmaceuticals was incompetent to provide any form of care in this situation, as a meager attempt to avoid a black box warning gave little insight to the physicians and patients about the dangers of this drug, clearly demonstrating how Wyeth acted in an unethical manner in their actions and attitudes towards this situation.

Conclusion:

To evaluate whether an individual or a group provided ethical care, Joan Tronto outlines four essential criteria: attentiveness, responsibility, competence, and responsiveness. While responsiveness does not apply in this case, the evidence shows how Wyeth Pharmaceuticals neglected to meet the remaining three criteria. From this, I argue that Wyeth Pharmaceuticals acted unethically in their response and actions to the fen-phen drug combination. While many have acknowledged the legal liability of Wyeth's actions, far less attention has been given to the ethical implications of their wrongdoings. An ethical analysis of Wyeth Pharmaceuticals is essential to deepen the understanding of their role in this case and understand how a lack of care can lead to dangerous negligence. It is vital to hold these companies to a higher ethical standard,

given their access to privileged information and how their actions have the potential to impact one's health. Gaining a greater understanding of how companies can violate their responsibility of ethical care can guide future efforts of holding these companies to higher standards, helping to prevent negligence and increase transparency, safety, and trust in the pharmaceutical industry.

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