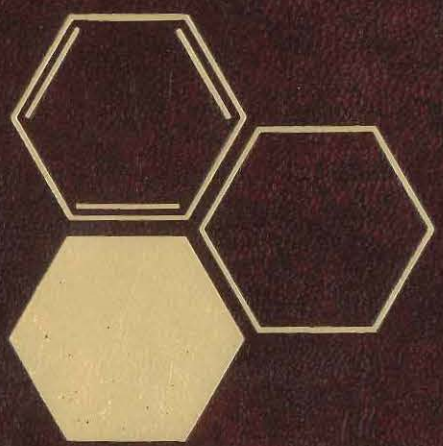
Drug Injury

Liability, Analysis and Prevention

Second Edition

James T. O'Donnell



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Chapter 28

The Rezulin Litigation

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Synopsis

Rezulin was a prescription medication for type-II diabetes developed by the Parke Davis division of Warner Lambert. Rezulin was a member of a new glass of diabetic medications known as thiazolidinediones or glitazones. The first drug in this class of drugs, a compound known as Ciglitazone, was initially developed by the Japanese company Takeda in the early 1980s as a cholesterol-lowering drug. Takeda was surprised to find that the drug also lowered blood sugar. Following this discovery, several companies started testing hundreds of related compounds in an effort to develop a drug with the demonstrated sugar lowering benefit without overriding risk.

Sankyo, another Japanese company, first studied Rezulin (Troglitazone) in the late 1980s. Sankyo filed an Investigational New Drug Application (IND) with the United States Food and Drug Administration (FDA) in 1989. In 1992, Warner Lambert bought a license to market Rezulin in the United States from Sankyo and took over the research and development of the drug in this country. Rezulin gained FDA approval in January of 1997 and was removed from the market in the spring of 2000 because of its severe liver toxicity.

This chapter will review first what science and medicine has shown is the type and scope of Rezulin's adverse effects. Before an individual case proceeds to trial, the litigator must have a clear and comprehensive knowledge of the medical issues involved with the drug. Much of that preliminary information comes from discovery into the drug manufacturer's own scientific and medical research. The chapter will summarize some of what discovery in the litigation has shown that Warner Lambert knew about these adverse effects and the timing of such knowledge. Indeed, internal corporate documents confirm that, at each stage of the drug's development, there was consistent evidence of the Rezulin's potential for liver toxicity but that Warner Lambert repeatedly chose to ignore, and in some cases cover-up, those signals in order to achieve blockbuster sales.

28.1 Identifying and Understanding a Rezulin Injury

A. The medicine

Rezulin is a drug that is toxic to the liver. There is no longer any real debate about that fact. Indeed the drug's significant liver toxicity led to its market withdrawal in 2000. What is less clear and still largely contested are the issues of

- how Rezulin causes injury,
- what a Rezulin liver injury really looks like, and
- whether Rezulin injures organs other than the liver.

Publicly, Warner Lambert took the position that Rezulin caused only a rare, idiosyncratic injury to the liver that is detected on blood test as a dramatic increase in liver enzyme levels. Warner Lambert, in essence, created the scientific knowledge about Rezulin, and in doing so, defined a "Rezulin injury" in a very limited way. Physicians relied on the Warner Lambert science and became conditioned to view Rezulin's injury risk in the same limited way.

The critical aspects of the Warner Lambert public description of a Rezulin injury are:

- injures the liver only,
- rare incidence (1 in 60,000 serious liver events[1]),
- idiosyncratic injury (unpredictable and of unknown cause),

- characterized by dramatic increase in liver enzyme levels on blood test,
- reversible except in the very rare cases,
- unknown mechanism of in jury,[2]

Interestingly, the science in Warner Lambert's own internal (non-public) documents contradicts the company's public definition of a Rezulin injury. There is a true dichotomy between what the company knew and what the company told. Warner Lambert consistently failed to release complete and accurate information about Rezulin's risks. Understandably, the medical and scientific communities relied on what they were told. It has taken doctors and scientists years to begin to question what they had been led to believe.

Warner Lambert's scientific deception had a similar impact on the litigation. Lawyers all over the country screened cases according to criteria they took from the existing published medical articles about Rezulin injuries. There was almost universal acceptance of Warner Lambert's position, which defined a Rezulin injury case as one involving a severe liver injury and high elevations of liver enzymes. It is only in the last year that lawyers have begun to challenge the company-created science.

Even with the recent challenges from the medical and legal communities, the story of Rezulin has been one of blockbuster success for Warner Lambert the senior management on the Rezulin project. The plan from the beginning was to deny the bad, overstate the good and keep control of the science as it developed about Rezulin. The result was a massive campaign of misinformation that contaminated the medical literature.

One of the earliest and best examples of this plan was the key marketing statement Warner Lambert consistently used to describe the risk of the drug. Initially, Warner Lambert denied that Rezulin had any real safety issues and in fact sought approval of their new drug on the basis of representations that Rezulin had a side-effect profile comparable to placebo (Figure 28.1).[3]

This marketing representation was soon proven false as people reported to hospitals with liver failure leading to death or requiring liver transplants. When it was no longer possible for Warner Lambert to deny the drug's toxicity, the company acted quickly to define that toxicity as set out above. The truth, which has now been confirmed from the discovery of Warner Lambert own scientific documents, is that the nature, scope and frequency of a Rezulin injury is much broader than the company was ever willing to admit publicly. We now know that

- Rezulin injures organs other than just the liver;

Summary: Safety Profile

- Adverse events comparable to placebo

Figure 28.1

- the incidence rate is not rare (e.g. Warner Lambert internal calculations show that one in 200 Rezulin patients reported a serious liver injury[4] and one in 550 Rezulin patients reported a serious episode of congestive heart failure[5]);
- the damage is not idiosyncratic alone since the mechanism of injury is known and shows a direct toxic effect on human cells;
- the damage occurs in the absence of increased liver enzyme levels and can be biochemically silent;[6]
- the damage does not always reverse on discontinuation of the Rezulin, and in fact many people actually suffered greater injury or further de-compensation after they stopped taking Rezulin;[7] and
- the damage has an understood mechanism of injury due to a toxic insult to the mitochondria of the human cell.[8]

B. Rezulin: A breakthrough drug for type-II diabetes?

The disease of type-II diabetes is characterized by a condition referred to as insulin resistance. Insulin resistance describes a condition where the body, initially at least, produces and circulates a sufficient amount of insulin however the cells are somehow closed off or resistant to the insulin. The insulin circulates in the blood but does not enter the cells.

Before Rezulin, there were only four different treatments for type-II diabetes:

- diet and exercise alone;
- sulfonylureas a class of oral medications that prompted the pancreas to work harder to produce more insulin;
- Metformin, an oral agent in the biguanide class that caused the body to more effectively use the insulin it had and produce less sugar; and
- insulin injections, which artificially supplemented the body's natural insulin production.

Warner Lambert claimed that Rezulin represented a breakthrough in the treatment of type II diabetes because it forced the cells to open up and better accept the circulating insulin. Warner Lambert claimed that Rezulin inhibited the body's sugar production, increased the amount of sugar the

body burned as fuel by the muscles and in this way "unlocked the cells" to the insulin and sugar circulating in the blood. What Warner Lambert did not explain was how Rezulin unlocked the cell and lowered blood sugar. Time and discovery into internal corporate documents would show that the drug only worked by injuring the cell's mitochondria.

C. Rezulin poisons the mitochondria

The mitochondria are the powerhouse of the cell. The mitochondria are that part of the cell that burn fuel to produce the energy the body needs to function and survive. Every cell in the body (except the mature red blood cell) has hundreds of mitochondria. Rezulin lowers blood sugar by poisoning the mitochondria of the cell.[9] This fact becomes the key to understanding all of Rezulin's effects on the body.

When the mitochondria are damaged, the cell produces less energy. As the damage increases, first the cell and then the organ itself will fail. One result of mitochondrial damage is that the body shifts to an alternate way of making energy called glycolysis. Glycolysis uses a lot more blood sugar than mitochondrial energy production. The result of this process of impairment and injury to mitochondrial energy production and a shift to glycolysis is lowered blood sugar levels.[10] Thus Rezulin appears to have the desired effect of lowering blood sugars in diabetics but this effect is achieved only through injury. Rezulin is like a weight loss program where a person does weigh less but only because they have had a limb amputated—the loss of pounds is achieved through injury to the body.

But damage to the mitochondria causes more than just lower blood sugars. The mitochondria produce critical energy for the cell to function and survive. If the mitochondria are damaged or disrupted the cell will not function correctly and eventually will die. When enough cells have died or stopped functioning correctly, the affected organ will begin to suffer dysfunction and eventually will fail. A Rezulin mitochondrial injury therefore, can appear as anything from single cell dysfunction and death to complete organ failure.

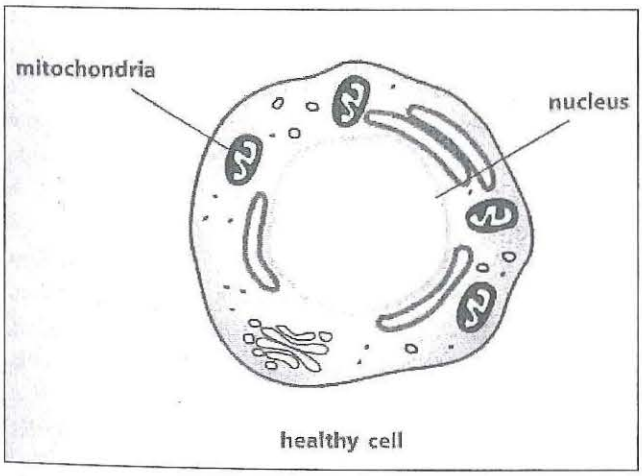


Figure 28.2 Healthy cell

1. Injuries from mitochondria damage

The early phases of a Rezulin mitochondrial injury are characterized by cell and organ dysfunction. The impairment in mitochondrial energy production limits the organ's ability to perform its functions. Depending on which organ is affected there can be a varied clinical presentation by the patient.

The liver for example performs over 500 different and essential functions. It metabolizes food and drugs, it detoxifies the body and removes the toxic waste through the biliary system, and it is the primary organ for the production, storage and regulation of glucose. Some of the most common manifestations of Rezulin-induced liver dysfunction are shown in Table 28.1. These conditions are hallmarks of drug-induced mitochondrial injury.[11]

2. Rezulin-induced cell death

As mitochondrial injury becomes more widespread, the cell will begin to swell and die. The two recognized types of cell death are apoptosis and necrosis. The generally accepted distinction between the two involves the number of cells that die at once and the amount of inflammation associated with the cell death. Both types of cell death result from injury or disruption to the mitochondria.[12]

Table 28.1
Some of the Most Common Manifestations of Rezulin-induced Liver Dysfunction

CONDITION	CAUSE
Steatosis (Fat in liver cells)	Injured mitochondria do not metabolize and burn the fat so the fat accumulates in the cell.
Cholestasis (build up of bile in the liver)	Lack of energy from mitochondria leads to less energy to move bile across the liver for disposal resulting in a back-up of the bile.
Cell death through apoptosis	Cell injury with reduced energy leads to a controlled cell death with reabsorption by surrounding cells.
Cell death through necrosis	Cell injury with a complete loss of energy leads to explosive cell death that injures surrounding cells as well.
Lowered blood sugar	Lack of energy from mitochondria prevents liver from producing sugar and leads to release of stored sugar to be used in glycolysis.

3. Apoptosis

Generally, the term apoptosis refers to controlled cell death, generally involving isolated individual cells. These are cells that have suffered injury and have released a signal that they need to be eliminated. A cell undergoing apoptosis has been too injured to survive but still has sufficient energy to die in an orderly fashion without taking any its neighbors along with it.[13] As the cell dies it divides and is consumed by the body's phagocytic cells so that the cell contents do not spill out and injure neighboring cells.[14]

Apoptosis is a natural process that occurs every day as older cells die out to be replaced. Drug-induced apoptosis (as seen with Rezulin) involves cells dying at an increased or accelerated rate compared to normal cell death. This is why apoptosis is also referred to as "cell suicide."

4. Necrosis

Necrosis cell death involves a larger number of cells and generally includes inflammation.[15] Here the cells do not have sufficient energy to die in an orderly and controlled way. This is a more serious injury resulting from the cells opening up and spilling their contents onto neighboring cells causing entire sections of cells to die.[16] Warner Lambert publicly admitted that Rezulin caused only this type of liver injury. See Figure 28.3.

D. The range of Rezulin injuries

With Rezulin the damage to the mitochondria presented in a variety of different ways depending on a multitude of factors including time of exposure, pre-existing organ health, genetic predisposition, as well as dose and sex. This is consistent with drug-induced mitochondrial injury in general.[17]

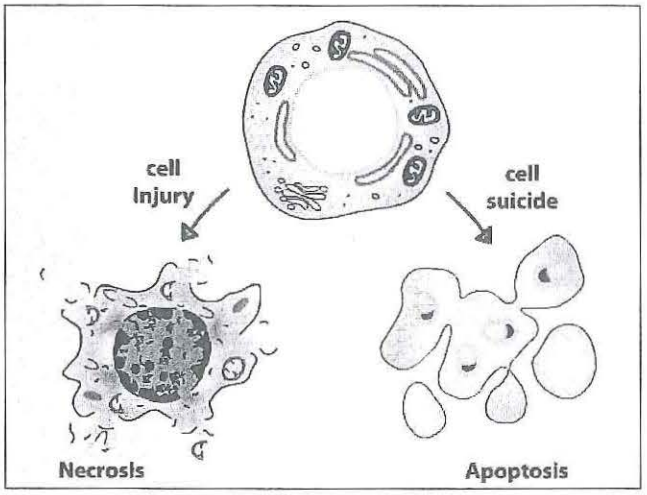


Figure 28.3 Cell death: necrosis and apoptosis

In contrast, Warner Lambert claimed that a Rezulin liver injury had specific clinical and biochemical characteristics primarily involving very high blood levels of the liver enzyme ALT. When a liver cell dies through necrosis and spills its contents into the blood, the ALT level in the blood will increase. Theoretically, the more cells that die and spill their contents, the higher the blood levels of ALT should be. In actuality, measuring the levels of ALT in the blood is only a crude estimate of the amount and severity of liver cell damage. Most agree there is very little correlation between the amount of cell death and the ALT in the blood. This is especially true with mitochondrial injuries.[18] Drug-induced mitochondrial injuries are characterized by ALT levels that are only mildly elevated if at all.

Mitochondria damage causes a range of injury and it can affect any organ in the body. Rezulin's primary target was the liver. Rezulin was metabolized in the liver and, was lipophilic (dissolves in fat) so it remained in the liver in high concentrations. It is estimated that the Rezulin concentrations in the liver were 12–20 times higher than that in the blood.[19] The calculated risk of a serious liver injury for patients taking Rezulin, assuming a 10-percent reporting rate, is 1 in 220 to 1 in 300. The FDA estimated that of those patients who took Rezulin for twelve months there was a risk that 1-2 out of 1,000 would die from acute liver failure from taking the drug.[20]

Rezulin injuries were not limited to the liver. The heart was also a frequent target of Rezulin-induced mitochondrial injury or disruption. When heart mitochondria are injured or nonfunctioning the reduced production of energy often presents as congestive heart failure (CHF).[21] Mitochondrial dysfunction leading to apoptosis is a leading cause of CHF.[22] Among patients taking Rezulin, there was a substantially increased risk of CHF as documented by Warner Lambert in its internal documents. The risk for patients taking Rezulin to have a serious episode of CHF was one in 550.[23]

28.2 What Warner Lambert Knew (and When) about Rezulin's Liver Toxicity

To get a drug approved by the FDA, the drug manufacturer must obtain and file scientific and medical evidence that supports the claim that the drug is both a safe and effective treatment. The medical and scientific data necessary to support approval comes from testing the drug company does over many years. The FDA does very little independent testing on drugs that are up for approval. In the case of Rezulin, the FDA did no pre-approval testing but instead, relied exclusively on the data provided by Warner Lambert.

There are clear, accepted stages that drug manufacturers must follow when developing a new prescription medication. These involve:

- **Class effect**. This involves a company researching the known strengths and weaknesses of all similar compounds in the same pharmaceutical class. With this knowledge, the drug developer can design studies to ensure that their proposed drug has the same or better benefits as other in the class without any, or with less, of the potential adverse effects.
- **Cell testing**. Drug manufacturers are required to do basic cell testing in order the gain FDA approval. If safety issues arise during this simple testing phase, many companies will repeat such tests or start more complicated cell studies to better understand the drug's mechanism of injury or effectiveness. Cell testing is relatively inexpensive and provides rapid answers to many questions of how the drug works.
- **Animal testing**. FDA requires animal testing in animal species before they will approve a new drug. Animal testing allows the company to sacrifice an animal and conduct detailed testing on each and every organ. Animal testing provides valuable insight into possible side effects of a drug and drug companies can then use their animal data to design human studies to confirm whether the same adverse effects are seen in humans or are unique only to the animal strain.
- **Human testing**. Human trials involve volunteer patients who take the prospective drug for a variety of time ranging from one pill to multiple months.

A. Class effect

In the late 1980s, several Japanese companies started developing a new class of diabetic medications known as the glitazones or Thiazolidinediones. In 1982, Takeda abandoned the first glitazone tested (a compound known as Ciglitazone) because of its liver toxicity.[24] In 1990, Pfizer discontinued their testing on Englitazone also due to that compound's adverse effects on the liver.[25] Warner Lambert clearly understood and appreciated the potential toxicity of this class. Indeed in 1995, two senior scientists on the Rezulin project, Dr. Randall Whitcomb and Dr. Alan Saltiel, published an article on the glitazones and wrote that prior glitazones "have yielded a side effect profile which has rendered them unacceptable for long-term human studies."[26] Despite this understanding, Warner Lambert never designed a single human study specifically to assess the drug's effects on the liver. When Warner Lambert's FDA expert, Dr. Thomas Q. Garvey, was asked whether the company designed a human study to look at the impact of Rezulin on the liver, he agreed that, "I don't remember a study with that specific objective."[27]

B. Cell testing

Warner Lambert conducted a number of Rezulin cell studies both before and after approval of the drug. These studies were designed to better understand the way Rezulin injured the liver cell. Warner Lambert's own studies confirm that Rezulin caused mitochondria damage as well as liver cell death through both apoptosis and necrosis.[28] Although these studies were conducted over several years, Warner Lambert chose to not publish the data until after Rezulin was removed from the market. Thus, throughout the time that the drug was being used, physicians had access to very limited, and largely distorted, published material about Rezulin and its ability to injure the patients.

C. Animal studies

Rezulin was tested in four animal species: rats, mice, dogs and monkeys. While animal data cannot be automatically extrapolated to humans, these studies provide important data on a drug's potential toxicity especially if the finding occurs in more than one species and at doses close to the human therapeutic dose equivalent. With Rezulin, liver problems developed in every animal species tested and at all doses,[29] low doses and even less than anticipated human dose. When expert panels for both the Australian and New Zealand regulatory agencies reviewed the Rezulin animal data, they confirmed the liver toxicity findings.[30]

As Warner Lambert's FDA expert, Dr. Thomas Q. Garvey, confirmed after his review of the animal data:

Q. So, based on the animal studies, there was evidence that the drug had liver toxicity potential?
A. Yes.[31]

Despite the animal results, Warner Lambert never conducted a human study to specifically assess Rezulin's impact on the human liver.

D. Human testing

Warner Lambert tested Rezulin on 2,510 human volunteers during the clinical trials.[32] While the company never conducted a specific liver effect study, they did complete blood testing on many of the participants. The blood panels provided some liver data such as liver enzyme levels. Because of the design of the human studies, Warner Lambert was able

2.17.24 Another Member with toxicological expertise supported previous speakers about the liver toxicity. The pre-clinical evaluator could not support the long term treatment of this drug because of the ubiquitous findings of hepatotoxicity in the four animal species which were mice, rats, dogs and monkeys. In contrast to that the Pre-ADEC response stated that there were no pre-clinical data reflecting hepatotoxicity. These statements were complete opposites and there was something amiss in the interpretation or in definition of what was meant by hepatotoxicity.

MEDICINES ASSESSMENT ADVISORY COMMITTEE

15 December 1998

C. Summary of the pharmacotoxicological data

Points which may be of concern are:

- limited exposure to troglitazone and metabolites in animals relative to that proposed in man
- the hepatotoxicity in rodents, dogs and monkeys

Figure 28.4 *In confidence extracts of the ratified minutes of the 199th (1998/5) meeting of the Australian Drug Evaluation Committee (ADEC) held on 1-2 October 1998*

to detect only the most obvious type of liver injury that is shown by elevated AST, ALT or Bilirubin levels.

Months after Rezulin was on the market, Warner Lambert told doctors that "during all clinical studies in North America, a total of forty-eight of 2,510 (1.9 percent) Rezulin-treated patients . . . had ALT levels greater than three times the upper limit of normal" and that two Rezulin patients developed reversible jaundice.[33] However, litigation review of the clinical trial data reveals that representation to be gross misrepresentations. Indeed, study data confirms that there were more than eighty patients with ALT levels greater than three times the upper limit of normal and four Rezulin patients who developed jaundice.[34] Interestingly, even when Warner Lambert disclosed a risk the disclosure was not accurate or complete.

Although clinical trials are often too small to detect rare adverse effects, the Rezulin human trials provided important medical information. Indeed, there were five liver related clinical deaths involving Rezulin patients. Each of these patients provided valuable medical information about the scope and nature of Rezulin injuries yet none of that evidence was ever disclosed to the physicians. Two examples are the NIH study death and the Reach study death.

In 1986, the National Institutes of Health (NIH) began a Diabetes Prevention Program. The goal of the study was to see if taking an oral diabetic medication prophylactically could reduce a person's risk of developing diabetes later. Thus the study participants were non-diabetic volunteers who agreed to take either oral diabetic medication or placebo. In May of 1998, Audrey Jones, a schoolteacher from St. Louis, Missouri, went into liver failure while a participant in the NIH study. She underwent liver transplantation but died a few days after the surgery. Both Warner Lambert and the NIH hired independent experts to review Audrey Jones' case. Both sets of experts agreed that Rezulin contributed to her liver failure and death.[35] This was important because Audrey Jones had been blood tested regularly and her liver enzymes routinely monitored. Despite this rigorous testing, Audrey Jones went into fulminant liver failure. Her death confirmed that liver enzyme monitoring could not protect patients. When the NIH stopped the Rezulin arm of the study because of the death, Warner Lambert was forced to issue a press release. In the press release, Warner Lambert denied that Rezulin played any part in the death and again purposefully mislead physicians about the drug's severe risks.[36] Warner Lambert stated in the press release that the patient died "apparently due to complications unrelated to the study or the medication."

After approval of Rezulin, Warner Lambert started a post-marketing clinical trial known as the Reach study. In December of 1998, a California Hispanic woman, and the mother of a famous jockey, died from liver failure. The patient had a history of alcohol consumption and likely pre-existing liver damage. Warner Lambert hired the same expert, Dr. Paul Watkins, to review this case. Dr. Watkins again confirmed that Rezulin "unquestionably contributed" to the patient's death.[37]

Warner Lambert never released any information about this death or warned physicians about avoiding the use of Rezulin in patients with pre-existing liver problems.

This omission seems remarkable considering that Rezulin was designed for a diabetic population where a large number of recipients would be already struggling with pre-existing liver problems.

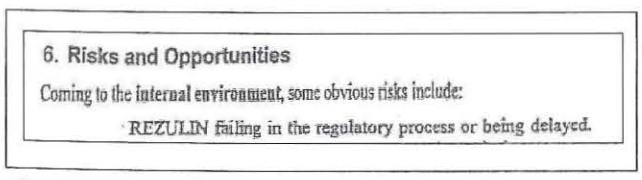
28.3 Warner Lambert's Reaction

Why then did Warner Lambert ignore every red flag? One explanation lies in the company balance sheets. In the early 1990s time frame, Warner Lambert was facing a financial crisis. They had experienced several years of flat sales, profitability well below industry averages, low stock value and the real threat of hostile take-over. In 1995, Warner Lambert pled guilty to and was convicted of a felony for intentionally falsifying documents filed with the Food & Drug Administration pertaining to the prescription drug Dilantin. The company paid a ten million dollar criminal fine and entered into a consent decree with the FDA, which resulted in the removal of several of Warner Lambert's products from the market. Warner Lambert assessed the financial impact of the consent decree at more than one billion dollars.[38]

In light of these financial setbacks, Warner Lambert's senior management needed Rezulin (and their other new drug Lipitor) to be blockbusters if they were to have any hope of saving the company. Warner Lambert recognized that Rezulin was capable of transforming "the fortunes of Parke Davis and through this the entire Warner Lambert company."[39]

As written by Anthony Wild, president of Parke Davis,[40] "1997 will probably be the most important year in the history of Parke-Davis, the year in which we begin our roll-out of the new products and troglitazone on which our future depends."

Anthony Wild further identified the Rezulin project as one that was "born of necessity: a sense of urgency created by the need for sheer survival."[41] Warner Lambert's own documents identify the importance of the Rezulin project and the true risks to the company should Rezulin fail to be approved.[42]


6. Risks and Opportunities

Coming to the internal environment, some obvious risks include:

REZULIN failing in the regulatory process or being delayed.

Figure 28.5 *A photocopy from a Warner Lambert document*

Rezulin's potential was enhanced because it was on schedule to be the first in its class to be approved in the United States. Warner Lambert understood the rewards of having the first glitazone approved.

Endnotes

1. Littlepage-Booth trial exhibit #227: Warner Lambert's "Dear Doctor" letter re: Rezulin, dated July 28, 1998.

2. Littlepage-Booth trial exhibit #165-173: Warner Lambert's package inserts for Rezulin.

3. Littlepage-Booth trial exhibit #1531: slide used by Dr. Randall Whitcomb during his presentation to the FDA Advisory Committee for approval of Rezulin; December 1996.

4. Littlepage-Booth trial exhibit #5125. Parke Davis Internal Memorandum, "Analysis of postmarketed spontaneous drug reaction data for Rezulin liver and/or CHF cases", dated January 27, 1999.

5. Littlepage-Booth trial exhibit #903: internal Parke Davis calculations re: "CHF executive summary," dated July 18, 1999.

6. Smith M.T., "Mechanisms of troglitazone hepatotoxicity," 2003 *Chemical Research & Toxicology*, Vol. 6, 679–687; Bonkovsky, "Severe cholestatic hepatitis caused by thiazolidinediones," 2002 *Digestive Diseases and Sciences*, Vol. 47, No. 7, pp. 1632–1637.

7. Littlepage-Booth trial exhibit #3593: Warner Lambert internal scientific memorandum, "Troglitazone-induced liver toxicity: Background summary and model hypotheses" by Thomas Woolfe, dated March 10, 1999.

8. Littlepage-Booth trial exhibit #5134: Haskins et al., "Thiazolidinedione toxicity to isolated hepatocytes revealed by coherent multiprobe fluorescence microscopy and correlated with multiparameter flow cyometry of peripheral leukocytes," 2001 *Arch. Toxicology* Vol. 75, 425–438; Littlepage Booth trial exhibit #3596: Tirmenstein, "Effects of Troglitazone on HepG2 Viability and Mitochondrial Function," 2002 *Toxicological Sciences*, Vol. 69, 131–138; Littlepage Booth Trial Exhibit #3795: Shishido, "Hydrogen peroxide overproduction in megamitochondria of troglitazone-treated human hepatocytes," 2003 *Hepatology*, Vol. 37, No. 1, page 136.

9. Littlepage-Booth trial exhibit #5134: Haskins et al., "Thiazolidinedione toxicity to isolated hepatocytes revealed by coherent multiprobe fluorescence microscopy and correlated with multiparameter flow cyometry of peripheral leukocytes," 2001 *Arch. Toxicology* Vol. 75, 425–438; Littlepage-Booth trial exhibit #3596: Tirmenstein, "Effects of troglitazone on HepG2 viability and mitochondrial function," 2002 *Toxicological Sciences*, Vol. 69, 131–138; Littlepage-Booth trial exhibit #3795: Shishido, "Hydrogen peroxide overproduction in megamitochondria of troglitazone-treated human hepatocytes," 2003 *Hepatology*, Vol. 37, No. 1, page 136.

10. Littlepage-Booth trial exhibit #3323: Shishido et al., "Cerebral oxygen and glucose metabolism and blood flow in mitochondrial encephalomyopathy: A PET study," 1996 *Neuroradiology*, Vol. 38, 102–107.

11. Littlepage-Booth trial exhibit #3327; Bissell, D. et al., "Drug-induced liver injury: Mechanisms and test systems," 2001 *Hepatology*, meeting report from American Association for the Study of Liver Disease, pp.1009–1013; Littlepage-Booth trial exhibit #3320: Farrell, G., "Drugs and steatohepatitis," 2002 *Hepatoxocity in the Twenty-First Century: Seminars in Liver Disease*, Vol. 22, Number 2; Littlepage-Booth trial exhibit #3321: Venediemale, G. et al. "Mitochondrial oxidative injury and energy metabolism alteration in rat fatty liver: Effect of the nutritional status," 2001 *Hepatology*, Vol. 33, No. 4, 808–815.

12. Littlepage-Booth trial exhibit #3326: Jaeschke, H. et al., "Mechanisms of hepatotoxicity," 2002 *Tox. Sciences*, Vol. 65, 166–176; and Littlepage-Booth trial exhibit #3327: Bissell, D. et al., "Drug-induced liver injury: Mechanisms and test systems," 2001 Meeting Report from American Association for the Study of Liver Disease.

13. Littlepage-Booth trial exhibit #3326: Jaeschke, H. et al., "Mechanisms of hepatotoxicity," 2002 *Tox. Sciences* Vol. 65, 166–176.

14. Littlepage-Booth trial exhibit #3325: Vermes et al., "Apoptosis: The genetically controlled physiological cell death: Biochemistry and measurement," *Ned. Tijdschr. Klin. Chem.*, 1997 Vol. 22, No. 2.

15. Littlepage-Booth trial exhibit #3325: Vermes et al., "Apoptosis: The genetically controlled physiological cell death: Biochemistry and measurement," *Ned. Tijdschr. Klin. Chem.*, 1997 Vol. 22, No. 2.

16. Littlepage-Booth trial exhibit #3934: Kaplowitz, "Biochemical and cellular mechanisms of toxic liver injury," 2002 *Seminars in Liver Disease*, Vol. 22, No. 2, page 137.

17. Littlepage-Booth trial exhibit #3327: Bissell, D. et al., "Drug-induced liver injury: Mechanisms and test systems," 2001 *Hepatology*, Meeting Report from American Association for the Study of Liver Disease, pp.1009–1013; Littlepage-Booth trial exhibit #3593: Warner Lambert internal scientific memorandum, "Troglitazone-induced liver toxicity: Background summary and model hypotheses" by Thomas Woolfe, Dated March 10, 1999.

18. Littlepage-Booth trial exhibit #3327: Bissell, D. et al., "Drug-induced liver injury: Mechanisms and test systems," 2001 *Hepatology*, Meeting Report from American Association for the Study of Liver Disease, pp.1009–1013.

19. Littlepage-Booth trial exhibit #3675: Toyoda, Y., Tsuchida, E. and Miwa, I., "Toxic effects of troglitazone on cultured rat hepatocytes," 2000 *Life Sciences* Vol. 68, pp.1867–1876.

20. Littlepage-Booth trial exhibit #3909: FDA's final report on Rezulin authored by Dr. David Graham; dated December 19, 2000.

21. Tsutsui, H. "Oxidative stress in heart failure: The role of mitochondria," 2001 *Intern. Med.* 40(12) 1177–82; Liu, P. and Sole, M.J. "What is the relevance of apoptosis to the myocardium?" 1999 *Can. J. Cardiol.* 1999 15 Suppl B:8B–10B; Shiraishi, J. et al. "Important role of energy-dependent mitochondrial pathways in cultured rat cardiac myocyte apoptosis," 2001 *Am. J. Physiol. Heart Circ. Physiol.* 281(4) 1637–47.

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23. Littlepage-Booth trial exhibit #5125: Parke Davis internal memorandum, "Analysis of postmarketed spontaneous drug reaction data for Rezulin liver and/or CHF cases," dated January 27, 1999.

24. Littlepage-Booth trial exhibit #2517: Gale, "Lessons from the glitazones: A story of drug development," *Lancet* 2001, Vol. 357, 1870–1875.

25. Littlepage-Booth trial exhibit #2613: Day, "Thiazolidinediones: A new class of antidiabetic drugs," *Diabetic Medicine* 1999, Vol. 16, 179–192.

26. Littlepage-Booth trial exhibit #3623: Whitcomb and Saltiel, "Thiazolidinediones: Oncologic, endocrine and metabolic section review," 1995.

27. Deposition of Dr. Thomas Q. Garvey, September 21, 2001, pp. 642–643.

28. Littlepage-Booth trial exhibit #5134: Haskins et al., "Thiazolidinedione toxicity to isolated hepatocytes revealed by coherent multiprobe fluorescence microscopy and correlated with multiparameter flow cyometry of peripheral leukocytes," 2001 *Arch. Toxicology* Vol. 75, 425–438; Littlepage-Booth trial exhibit #2559: Kostrubsky, V. et al., "The role of conjugation in hepatotoxicity of troglitazone in human and porcine hepatocytes cultures," 2000 *Drug Metabolism and Disposition*, Vol. 28, pp. 1192–1197.

29. Littlepage-Booth trial exhibit #917: Parke Davis Memorandum dated June 29, 1992 re: CI-991 Exploratory Development Team.

30. Littlepage-Booth trial exhibit #429: extracts of the ratified minutes of the 199th Meeting of the Australian Drug Evaluation Committee; Littlepage-Booth trial exhibit #441, New Zealand's Medicine Assessment Advisory Committee review.

31. Deposition of Dr. Thomas Q. Garvey, September 1, 2001, page 346.

32. Warner Lambert's package inserts for Rezulin.

33. Littlepage-Booth trial exhibit #165-173: Warner Lambert's package inserts for Rezulin.

34. Littlepage-Booth trial exhibit #2617A: internal Parke Davis memorandum, "Rate of elevated ALT levels by study month"; Littlepage-Booth trial exhibit #3663: internal Parke Davis memorandum titled "Monthly rate of ALTs being 3 times the upper limit of normal."

35. Littlepage-Booth trial exhibit #675: Letter from Dr. Paul Watkins to Warner Lambert re: assessment of NIH study death, dated May 28, 1998; Littlepage-Booth trial exhibit #671: Report of Committee of Hepatic Injury in patient AUJO (#172079) receiving Troglitazone in Control Trial.

36. Littlepage-Booth trial exhibit #2049: Warner Lambert press release, "Changes in NIH diabetes prevention program announced today," dated June 5, 1998.

37. Littlepage-Booth trial exhibit #50: transcript of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting, March 26, 1999, Dr. Paul Watkins' presentation to the Committee.

38. Deposition of President of Parke Davis, Anthony Wild, September 5, 2001, page 660.

39. Littlepage-Booth trial exhibit #1401: Anthony Wild memorandum, "Pharmaceutical sector 1997–2000 sector plan."

40. Littlepage-Booth trial exhibit #1409: Anthony Wild memorandum, "1997 Possible assumptions."

41. Littlepage-Booth trial exhibit #1415: Anthony Wild memorandum for senior management, "Some thoughts on possible R&D paradigms for Parke Davis," dated February 14, 1997.

42. Littlepage-Booth trial exhibit #1401: Anthony Wild memorandum, "Pharmaceutical sector 1997–2000 sector plan."