Would Acetaminophen be Approved by the FDA Today?

GEMS104 Drug Development and Regulation

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The Tragedy of River Moore

On July 22, 2010, Daniel and Katy Moore awoke to find their two-year-old son, River, coughing up blood only thirty minutes after they had administered a single dose of Very Berry Strawberry Children's Tylenol (Sell 2012; WDM Group PR Network 2012). Less than a day later, River was pronounced dead from liver failure. An autopsy ruled out viral pathogens and other pre-existing conditions as the cause of death and confirmed that the toddler's liver contained three times the normal level of enzymes, implicating the medication as the cause of death (The Associated Press 2012).

Wrought with grief and looking for answers and accountability, the Moore family sued the pharmaceutical giant Johnson & Johnson and its subsidiary, McNeil Consumer Healthcare, for negligence, breach of warranty, infliction of emotional distress, conspiracy, and the reckless production and distribution of Tylenol products containing higher-than-normal levels of its active ingredient, acetaminophen (The Associated Press 2012). Earlier that year, Johnson & Johnson had recalled Children's Tylenol and several other over-the-counter (OTC) drugs intended for infants and children, but had insisted that "the potential for serious medical events [as a result of the recalled medications was] remote" (The Associated Press 2012). The Moores' allegations are currently being investigated, but it is unlikely that the case will be closed for years to come, as Johnson & Johnson continues to defend its "billion-dollar revenue streams of pediatric medicines" (The Associated Press 2012; WDM Group PR Network 2012).

It is cruelly ironic that acetaminophen was originally *meant* to be a drug for infants and children, marketed as the "Tylenol elixir for children" (Bowden et al. 2003). Although the drug was first synthesized in 1877 at Johns Hopkins University by Harmon Northrop Morse (Morse 2006), it was not until 1947 that the efficacy of acetaminophen was proven through clinical trials

(Lester and Greenberg 1947). Acetaminophen was approved by the Food and Drug Administration (FDA) in 1955 as a therapeutic analgesic (pain killer), antipyretic (fever reducer), and weak anti-inflammatory drug (WHO 1999). A year later, it became an OTC drug (Bowden et al. 2003). Acetaminophen grew in popularity and production due to the massive efforts of the McNeil Company, Robert McNeil's pharmaceutical giant. This trend was continued by Johnson & Johnson, the massive pharmaceutical empire that purchased McNeil in 1959 (Molina et al. 2011). In 1968, the FDA re-evaluated all medications and acetaminophen was re-approved without further rigorous testing (FDA 2010a). Since then, acetaminophen has become available as the single active ingredient in countless single-agent dose formulations and delivery systems. It is also available in combination with other non-narcotic analgesics, narcotic analgesics, sedatives, decongestants, expectorants, and antihistamines (Goldfrank and Flomenbaum 2006). Some of these combinations include OTC drugs, such as Benadryl and Dayquil, and prescription medications including Vicodin, Percocet, and Tylenol with codeine (WHO 1999).

Although the first occurrence of acetaminophen-linked acute liver failure (ALF), was documented in 1966, it was not until the late 1990s when research began to prove a correlation between acetaminophen and ALF (WHO 1999; FDA 2011). Because more than half the cases of ALF were because of unintentional overdoses, the FDA began taking steps to reduce the frequency of liver injury related to acetaminophen dosing errors in adults and children (FDA 2011). This included labeling format changes, increased warning labels, and stricter dosage maximums. Evidently, these precautions have not been enough to prevent the deaths of both adults and children, including River Moore.

Such cases provide clear evidence of the danger associated with acetaminophen usage, which is often overlooked by the public (Bakalar 2007). Although River's parents' charge that

the specific batch of Very Berry Strawberry Children's Tylenol responsible for their son's death contained a higher-than-normal milligram amount of acetaminophen, River's story raises many concerns about acetaminophen regulation and usage even when the product is manufactured as intended. Does such a lethal drug, if used improperly, require public awareness and labelling campaigns to educate the public, especially parents, about the risks associated with acetaminophen usage? Should the level of acetaminophen in OTC drugs be more strictly regulated? Finally, should we be using existing alternatives that have less potential for danger?

We believe that society's long-term acceptance of the risk associated with acetaminophen usage risk constitutes "normalization of deviance," a term American sociologist Diane Vaughan coined in 1997 to describe a failure of foresight that results from the continuous act of ignoring deep concerns while making formal risk assessments that dismiss signs of danger (Vaughan 2004). This unintentional risk-creep is exacerbated until "predictable disasters" like the death of River Moore occur. Although River's story may seem shocking at first—two concerned parents simply gave their feverish infant Tylenol, and the child *died*—an investigation into the history of acetaminophen development and marketing, the mechanisms by which acetaminophen causes liver damage, the common patterns represented by past overdoses, and the metamorphosis of FDA regulations certainly indicate that this disaster could have been prevented.

The purpose of this paper is to explore the historical and social reasons why acetaminophen is so widely, and somewhat blindly, used by Americans. Considering the documented risks and current FDA policy, if acetaminophen had not been discovered so long ago, and had not become a staple in every American family's medicine cabinet, would the FDA approve it today? We intend to elucidate the reasons why acetaminophen usage constitutes risk, including the fact that the liver processes the drug into harmful metabolites. We also intend to

provide an overview of the "signs of danger" that Vaughn describes in her theory through examples of overdose case studies and recalls of products that contain acetaminophen. We will also evaluate how these signs of danger have been largely ignored by the public due to the FDA's weak response to these overdoses.

It is imperative that the FDA tighten regulations on acetaminophen dosage, increase awareness about the risks associated with acetaminophen usage, and recommend alternatives, such as aspirin, ibuprofen or naproxen sodium. Although each of these alternatives has its own side effects, it is evident that none of them have caused as many accidental overdoses as acetaminophen. There are currently other possible modifications to acetaminophen packaging and distribution that the FDA can enact to reduce the incidences of liver injury. This includes reducing the current dosage or restricting the current maximum daily dosages, creating packaging size limits for OTC acetaminophen products, and expanding product warning information to prescription medication. The FDA could also remove acetaminophen from combination OTC and prescription products. Thus, we plan to develop a set of recommendations regarding the FDA's regulation of acetaminophen that will take into account the many risk factors inherent in its usage. Addressing the need for a more comprehensive and thorough analysis of acetaminophen usage is a necessity. We must reveal the "normalization of deviance" surrounding acetaminophen in order to prevent future tragedies like the death of River Moore.

The Development and Growth of Acetaminophen

The history of acetaminophen-based products has influenced drug development and manufacturing even today. Tylenol and most acetaminophen-based products remain popular today, and its remarkable yet unsettled history offers profound insight into how a company as

well as the entire drug manufacturing industry has evolved over the last century. Initially synthesized by Harmon Northrop Morse at Johns Hopkins University in 1877, acetaminophen was subsequently developed by the McNeil Company (Morse 2006). Later, Johnson & Johnson Company purchased rights to the drug. Today, products containing acetaminophen dominate the drug industry and acetaminophen has seemingly become the preferred analgesic among consumers around the world. Despite humble beginnings, initial rejection, and malicious sabotage, acetaminophen-containing products have been shrewdly marketed by all of its owners, making it one of the dominant non-prescription pain relievers in pharmaceuticals today.

Synthesis and early clinical trials of acetaminophen

Acetaminophen, Morse's "miracle-drug," is known internationally as paracetamol. It is also formally referred to as *N*-acetyl-*p*-aminophenol in chemical nomenclature and is commonly abbreviated as APAP. It is a synthetic white crystalline powder isolated from coal tar (See *Figure 1*). It is considered an "aniline analgesic," and is the only such compound still used today.

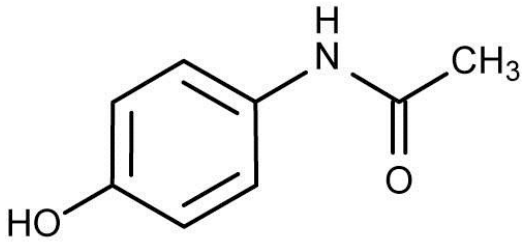

Figure 1: The chemical structure of acetaminophen.

When acetaminophen was first synthesized, several alternative analgesics and antipyretic drugs were already being experimented upon. At the time, many mixtures of compounds derived from natural sources such as cinchona bark and willow bark were used as antipyretics (PharmWeb 1994). However, scientists continued to attempt to find a better drug capable of lowering fever. Two aniline analgesics, acetanilide and phenacetin, were developed in 1886 and

1887, respectively (PharmWeb 1994). Both alternatives had antipyretic and analgesic properties and were viewed as more effective than any natural combination product (PharmWeb 1994).

Still, questions surrounding the true makeup of these drugs remained. It was proven in 1889 that acetaminophen was a major urinary metabolite of acetanilide (PharmWeb 1994). When metabolized by the body, acetanilide is partially converted to both acetaminophen and aniline, the latter being toxic in moderate doses(Imperial College of London). This toxicity created from the by product aniline made acetanilide a deadly analgesic. Clearly, the other main metabolite, acetaminophen, showed promise as a possible new drug. It was accepted that acetaminophen was causing the primary painkilling properties and that it was a fine alternative, but lingering qualms about its effects remained (Imperial College of London).

In 1893, Joseph von Mering, a German physician, began experimental trials of acetaminophen on patients and discovered that acetaminophen caused methemoglobinemia, a blood disorder that produces abnormal levels of methemoglobin, which impairs the hemoglobin of the red blood cells, thereby reducing the oxygen carried and released to blood tissue (Bertolini 2006). Von Mering's discovery led to a general abandonment of acetaminophen in favor of phenacetin, leaving acetaminophen off the shelves and out of scientific research for roughly fifty years (Chemical Heritage Foundation). However, in 1947, two Americans named David Lester and Leon Greenberg produced studies that showed that acetaminophen use did not result in methemoglobinemia (Greenberg et al. 1947). In fact, in 1948, Julius Axelrod and Bernard Brodie discovered that acetaminophen was a major metabolite of both phenacetin and acetanilide, which indicated that rejecting acetaminophen in favor of phenacetin was misinformed (PharmWeb 1994). Additionally, this confirmed that the analgesic effects from phenacetin and acetanilide were caused by its rapid breakdown into acetaminophen, the compound responsible for the

reduction of prostaglandin, which reduces the dilation of the blood vessels causing an ultimate reduction of pain (Imperial College of London). Understanding this led to the idea of making purely acetaminophen based products. Moreover, since acetanilide and phenacetin had to be administered in large, often unsafe doses to obtain the real analgesic effect, it was favorable to mass produce the acetaminophen itself.

Brodie's and Axelrod's discovery led to the introduction and subsequent widespread use of the 500 milligram tablet of acetaminophen in the UK in 1956, where it was sold as primarily a prescription product (PharmWeb 1994). In 1963, acetaminophen-based products were added to British Pharmacopoeia, the official source of British pharmaceutical standards, and its popularity grew astronomically in the UK (British Pharmacopoeia 2012).

Initial development by the McNeil Company

Meanwhile, in the United States, the development of acetaminophen was also growing through the efforts of Robert McNeil Jr. and his pharmaceutical company, the McNeil Company. Just as interest piqued in the UK regarding the mass production of acetaminophen around the 1950s, researchers throughout the United States began to take interest in acetaminophen and started conducting studies to demonstrate its safety as an analgesic and antipyretic (Chemical Heritage Foundation). In 1954, at the discretion of Robert McNeil Jr., McNeil Laboratories of Philadelphia seized the opportunity to profit from this new product.

Long before it found acetaminophen, however, the McNeil pharmaceutical empire began as a simple drugstore purchased in 1879 for $167 by Robert McNeil (McNeil Consumer Healthcare). This drugstore located in the heart of the mill district of Philadelphia was a profitable enterprise and was known for its high quality of work, which helped pave the way for many future business opportunities for the McNeil family. In the early 1900's, McNeil and his

son Robert Lincoln McNeil partnered together and decided to expand the business and focus on drug research and production (McNeil Consumer Healthcare). In 1925, the pharmaceutical company expanded once again, moving to a large plant equipped with the most modern equipment designed for manufacturing (Chemical Heritage Foundation). Led by Robert McNeil, Jr. and a team of young recruits, the McNeil Company set out to develop new products and market them to the public. McNeil, Jr. was instrumental in remodeling of the company's product line, reorganizing of its departments, and creating a world class research division that made products that complied with the Food & Drug Cosmetic Act of 1938 (Bowden et al. 2003).

In the early 20th century, members of the Progressive movement, including prominent intellectuals, questioned the lack of adequate treatment of consumers in many prominent US industries, including cosmetics, food, and drugs. The 1933 piece of muckraking journalism *100,000,000 Guinea Pigs* by Arthur Kellet and F. J. Schlink suggested that American consumers were constantly being used as test "guinea pigs" for products sold by these companies, essentially letting these giant corporations poison them (Kellet and Schlink 1933). A major discussion point in the exposé concerned the practices of the FDA and the ineffective nature of the Administration's laws in combating the problem of safe pharmaceuticals. Kellet and Schlink explored the sheer dishonesty and fraudulent techniques drug manufacturers at the time were using to market their products, which sometimes had fatal consequences for consumers. *100,000,000 Guinea Pigs* was instrumental in the passage of the new Food, Drug, and Cosmetic Act (FDCA) of 1938, which protected consumers from the rampant abuses of major industrial corporations (Kellet and Schlink 1933). Consumers were outraged at the apparent exploitation by these giant corporations and wanted to have access to safe, reliable products instead.

Given this rising sentiment and the new regulations of the FDCA, Robert McNeil Jr. turned to a seemingly safe, relatively unexplored alternative, acetaminophen. His interest in acetaminophen was especially piqued after talking with Robert Conklin, vice president at the Institute for the Study of Analgesic and Sedative Drugs, at the Pharmaceutical Manufactures Association meeting of 1939. The Institute had been researching the substance and had found some evidence supporting that acetaminophen was largely free major side effects when taken in normal dosages. Papers published by the Yale College of Medicine and New York University had proven the merits of acetaminophen usage, but efforts to forcefully market the product were limited because companies did not want to diminish the sale of aspirin, the dominant analgesic at the time. Yet McNeil was convinced of the potential for acetaminophen to be a viable alternative to aspirin. McNeil Company's medical science division and clinical investigation team later confirmed results from Conklin's report, which lead to the rise and development of the world's most prominent analgesic (Chemical Heritage Foundation).

After his meeting with Conklin, he met with his New Products committee, which included both scientists as well his brother (head of the marketing division) and the directors of sales, marketing, advertising and promotion, where he presented the idea of marketing acetaminophen-based products. McNeil was faced with the question of how they would compete against aspirin and whether the company could seriously profit from it. McNeil believed that his acetaminophen-based products would be different from aspirin in one important regard: it would not cause the immense stomach irritation that aspirin caused (Chemical Heritage Foundation). Additionally, the McNeil Company initially marketed its products as prescription medications, not as OTC medications, essentially eliminating the competition against aspirin (Bowden et al. 2003). Throughout the 1940s and early 1950s, the lack of competition let the McNeil Company's

products flourish, primarily targeting the field of pediatric medicine (Chemical Heritage Foundation). Clinical Trials were conducted for the Children's Elixir product in which doctors and scientists confirmed the early claims of aspirin's erosion of the stomach lining, even when taken in moderate doses. Finally, in 1955, Tylenol Elixir was released and marketed to children in miniature paper fire truck boxes with the slogan "For Little Hotheads" (See cover photograph) (Bowden et al. 2003).

Further development by Johnson & Johnson

McNeil Company was purchased by Johnson & Johnson (J&J) in 1959, becoming a subsidiary of J&J and beginning another long dynasty in Tylenol history. During the J&J era, Tylenol products went through turbulent stages, but the company was able to instill tremendous public trust in their acetaminophen products through shrewd business strategies. In 1960, the McNeil Company sold the first non-prescription bottle of Tylenol (Molina et al. 2011). In the early years of Tylenol under J&J's leadership, it was through the actions of James Burke, the president of J&J's Domestic Operating Company in 1966, that Tylenol experienced tremendous growth. Tylenol had always been an expensive product, but Burke saw the need to lower its price to compete with one of the leading alternatives, Datril, marketed by Bristol-Myers. Burke convinced J&J chairman Richard Sellers to lower the price, which catapulted Tylenol into the mass-marketing arena, eventually beating out Datril and other alternatives such as the number one Anacin product. Burke eventually succeeded Sellers as the chairman of J&J in 1976 and began the aggressive marketing of many consumer products, especially Tylenol, earning it a position on the J&J number one seller list and making it one of the most popular OTC drugs in the nation (Salamie et al. 2006).

Consumer trust in Johnson & Johnson

Although it may seem ironic in the face of accusations of acetaminophen toxicity today, J&J was very unique in implementing and following a code of ethics, a feature not seen in many corporations at the time. Robert Wood Johnson, who was the chairman of J&J from 1932 to 1963, was instrumental in developing one of the most influential code of standards, "Credo," which was intended to maintain an "ethical corporate culture" and ensure the economic success of the company (Molina et al. 2011). The Credo states that the company's first responsibility is to meet the needs of all doctors, nurses, patients, mothers, fathers, children, and consumers (Johnson & Johnson 1943). J&J's Credo has been an important decision-making tool in most situations in the company, placing prime importance on the consumer (Molina et al. 2011).

This was especially true after the tragic cyanide poisoning incidents in 1982. On September 29, 1982, when a Chicago area 12-year-old, Mary Kellerman, and three others took Tylenol capsules laced with a shocking 65 milligrams of cyanide. It was later found that the deaths were not the result of sabotage during production, but the work of culprits entering individual supermarkets and drug stores and replacing the contents of Tylenol packages with cyanide (Molina et al. 2011). This was a challenge that J&J faced with extraordinary poise without destroying any credibility of the company.

Burke defied the advice of government agents and spent over $100 million to recall nearly 31 million bottles of Tylenol capsules across the country. This process was opposed by the FDA and other federal organizations, which speculated that the recall would cause immense public fear and the demise of the company. However, Burke's move proved to be a smart business decision, restoring the confidence of potential customers. The week after Burke's announcement, Tylenol regained over 80% of its market share, which was called a "miracle" by

many financial experts. In accordance with the Credo, J&J and McNeil Consumer Products were not defensive about their mistakes and actively investigated the cause of the crisis. J&J even gave away more than $80 million in coupons to consumers to use on Tylenol products and aired numerous testimonial-style television ads claiming that Tylenol was reliable and trustworthy (Time Magazine 1983). Moreover, almost 2,250 salespeople presented to members of the medical community to help restore their trust (Molina et al. 2011). After this, Tylenol's market share climbed back to 30%, a figure that was close to what it had before the incident (Time Magazine 1983). The Credo has served J&J well, making Tylenol one of the most widely trusted and used analgesic products in the market today.

J&J has continued power and influence on consumers around the world. In fact, a 2005 Reputation Survey conducted by the Harris Interactive ranked J&J as the number one most trusted corporation by consumers (Harris Interactive Inc. 2005). This has directly translated to high sales of Tylenol and high profits for J&J. As of 2005, more than 28 million doses of acetaminophen-based products were purchased. In fact, it has been the most purchased drug since 1997. Single-ingredient OTC products represented 8 million doses in 2005, while combination OTC products accounted for 9.7 billion. The use of acetaminophen-containing prescription narcotics increased almost 38% between 2001 and 2005, representing 11 billion total doses during the time period (FDA 2011a).

Although these statistics represent overall consumer support and trust of J&J products, recent consumer opinion reveals an opposite trend, owing largely to production issues. From the fall of 2009 to early 2010, there have been a number of unsatisfactory inspections of the company's facilities, where problems included faulty laboratory equipment, excessive bacteria in certain OTC liquids, and improper maintenance of McNeil facilities (FDA 2010c). The aftermath

of the River Moore incident exemplifies some growing distrust in Tylenol products due to acetaminophen-induced ALF. River's parents issued a strong claim against the company, claiming J&J performed a "secret recall" of defective products without informing the public to save its reputation and profits. If the recall, which was enacted before River Moore's death, had been made public, River's parents would have known not to give their child the defective Very Berry Children's Tylenol. Accordingly, the complaint report blamed the McNeil Company for absolute negligence and clandestine practices at the expense of innocent consumers (Harris 2012). At a 2010 Congressional Oversight Hearing in response to the recall, McNeil officials admitted that the company did not live up to its responsibility toward doctors, nurses, patients, mothers and fathers, and all users of their products: a blatant violation of the Credo (Messa & Associates 2010). These incidents show a continued culture of negligence within J&J, its subsidiary McNeil, and its factories, which certainly does not live up to J&J's supposed Credo.

J&J has also also promoted a normalization of deviance while responding to the rising cases of ALF. In 2009, an FDA advisory panel called for new limits on the sale of acetaminophen, including the possibility of lowering the accepted daily dose from from 4,000 milligrams to 2,600 milligrams and making Extra Strength Tylenol a prescription-only medication. J&J publicly stated that the company "strongly disagreed" with this recommendation, despite the fact that cases of ALF due to acetaminophen overdose have been documented for over fifty years (Goldstein 2009).

The Etiology and Pathophysiology of Acetaminophen Overdose

Understanding the chemical mechanisms by which acetaminophen toxicity occurs reveals some of the ways in which acetaminophen overdose can be prevented and assists in answering the question of whether acetaminophen is dangerous enough to be more tightly regulated. When

the first cases of acetaminophen-linked hepatotoxicity were reported in 1966 followed by numerous others, an "intensive research effort clarified the metabolic basis of both the pharmacologic safety and the toxicologic danger of acetaminophen" (WHO1999; Goldfrank and Flomenbaum 2006). Many of these studies involved knocking out specific genes that code for the enzymes that metabolize acetaminophen in mice and hamsters, homologous to those in humans (WHO 1999). It was found that the safety of acetaminophen ingestion and metabolism relies on the presence of glutathione (GSH) (See *Figure 2*), a natural antioxidant present in the liver, and other compounds containing thiol (-SH) functional groups, which serve as stable electron donors that prevent further free radical reactions from occurring (Goldfrank and Flomenbaum 2006).

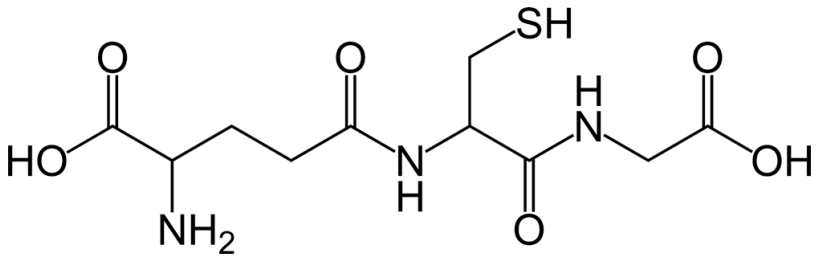

Figure 2: The chemical structure of glutathione.

Through these methods, the major pathways that cause hepatotoxicity (liver damage) and nephrotoxicity (kidney damage) were elucidated. Many of these pathways initiate oxidative and free-radical reactions that cause damage to the liver and kidneys (WHO 1999).

The major metabolic pathways of acetaminophen

The dosage at which drugs are effective is measured in serum concentration, or the amount of the drug in circulation in the blood (both bound and unbound to proteins). Acetaminophen exhibits antipyretic activity at a serum concentration anywhere between 4-18

micrograms/milliliter, and is an effective analgesic at a serum concentration of 10 micrograms/milliliter. The peak activity of orally ingested liquid acetaminophen occurs in 30 minutes, while immediate-release acetaminophen capsules achieve their effect in approximately 45 minutes. The majority of acetaminophen absorption through the stomach and small intestine occurs within two hours of ingestion (Goldfrank and Flomenbaum 2006).

Because the body recognizes that the ability to feel pain is beneficial to its survival, the body tries to detoxify acetaminophen immediately after absorption. Acetaminophen is metabolized by conjugation in the liver to inactive, water-soluble metabolites that are excreted in the urine. First-pass metabolism, or the immediate degradation or alteration of the drug by hepatic enzymes and intestinal enzymes before it reaches systemic circulation, removes approximately 25% of the therapeutic dose and begins metabolizing it. When the drug is metabolized by the body, approximately 90% of the therapeutic dose is conjugated with glucuronic acid and sulfate, two other antioxidants in the liver, to form the non-toxic metabolites that are excreted by the kidneys (See *Figure 3*). Less than 5% of therapeutic dose is excreted unchanged (Goldfrank and Flomenbaum 2006).

The remaining 5-15% of therapeutic dosage is oxidatively metabolized by members of the cytochrome P450 (CYP) superfamily, a group of enzymes responsible for metabolizing lipids, steroidal hormones, and drugs to the toxic metabolite *N*-acetyl-*p*-benzoquinoneimine (NAPQI) (See *Figure 3*). The major actor in this pathway is CYP2E1, with small contributions from CYP3A4, CYP2A6, and CYP1A2 (Goldfrank and Flomenbaum 2006). CYP2D6, which is responsible for the metabolism of 25% of drugs on the market today, has also been shown to metabolize acetaminophen to NAPQI (Aulinskas 2010; Dong et al. 2000).

In non-overdose situations, this is not so problematic because NAPQI is quickly conjugated with GSH and other thiol-containing compounds, and these conjugates are in turn converted to non-toxic cysteine and mercaptate conjugates, meaning that they are bound to sulfur-containing amino acids. These conjugates are then renally excreted (Goldfrank and Flomenbaum 2006).

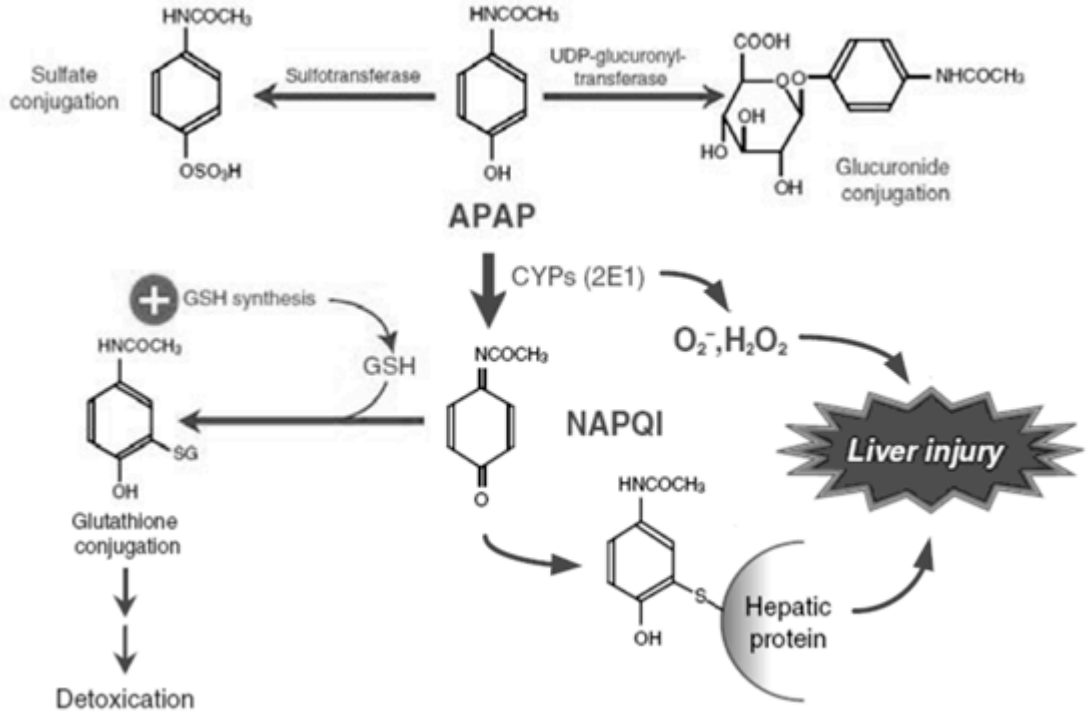

Figure 3: Major metabolic pathways of acetaminophen (Guzikowski et al.).

The danger of hepatotoxicity, commonly known as liver failure, occurs when the major non-toxic metabolic pathways become saturated and the excess acetaminophen is diverted to the metabolic pathway that forms NAPQI (Goldfrank and Flomenbaum 2006). This saturation amounts to a single ingestion of 150 milligrams/milliliter, or approximately 7,000-10,000 milligrams of acetaminophen in adults (Beck 2009). The sulfate conjugation pathway is the primary capacity-limited pathway; although the glucuronidation pathway was initially thought to be saturable, it is now accepted that this pathway is only saturated in "severely poisoned

patients" (WHO 1999; Goldfrank and Flomenbaum 2006). It has been confirmed that "the amount of NAPQI formed is increased out of proportion to the acetaminophen dose because maximal rates of sulfation are exceeded" (Goldfrank and Flomenbaum 2006). As the concentration of NAPQI builds up in the liver, GSH stores are depleted. When 70% or more of these stores are depleted, NAPQI covalently bonds to various macromolecules including cellular proteins, causing oxidative damage, mitochondrial dysfunction, and a subsequent inflammatory response that leads to hepatocellular injury, kidney damage, liver necrosis and eventually death (Goldfrank and Flomenbaum 2006).

There are many different environmental factors that may exacerbate acetaminophen toxicity in individuals by increasing cytochrome P450 enzyme activity, thereby increasing NAPQI concentration. For instance, CYP2E1 is also activated by ethanol consumption, starvation, diabetes, and premutagens in cigarette smoke (NCBI 2012). In short, individuals who are malnourished or dehydrated, have a history of chronic alcohol abuse, are suffering from viral illness, or have recently ingested other medications that induce CYP enzyme activity are more susceptible to acetaminophen hepatotoxicity.

Poor, intermediate, and ultrarapid metabolizers

Genetic variation in the genes that encode CYP enzymes also has a profound effect on acetaminophen metabolism in individuals. Many of these genetic variations appear in the form of single-nucleotide polymorphisms (SNPs, pronounced "snips"), defined as "positions in the genome where people vary in a single nucleotide base." These polymorphisms, identified by the Human Genome Project, are called haplotypes and are inherited as allelic variants like any other gene. Most of the time, SNPs do not produce a noticeable phenotypic difference due to the redundancy of the genetic code (Pierce 2012). However, SNPs in enzymes involved in the

absorption and metabolism of drugs can have significant effects on the body's reaction to pharmaceuticals including acetaminophen. When the SNP occurs in a promoter site, transcription and translation can be heightened, reduced, or lost completely. Additionally, if SNPs are located in the coding region of a gene, "there is an alteration in the amino acid sequence of an enzyme that directly or indirectly influences function" of the enzyme (Flaherty 2007). While there is much SNP variation in CYP2E1, CYP2D6 has the most documented genetic variation, perhaps due to the fact that it is activated by 25% of common drugs, including serotonin reuptake inhibitors, tricyclic antidepressants, beta blockers, opiates, neuroleptics, antiarrhythmics, and, of course, acetaminophen (Sim; Aulinskas 2010).

In fact, there are over 90 known allelic variants of CYP2D6. Four phenotypes that describe ability to metabolize drugs have been identified. They are, in order of lowest to highest function, poor metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs), and ultrarapid metabolizers (UMs) (PharmGKB 2012). While EMs are phenotypically normal, PMs and IMs are unable to metabolize acetaminophen as effectively, resulting in higher plasma levels of the drug, which is eventually diverted to harmful metabolic pathways. Ultrarapid metabolizers possess a copy number variation ("a difference among people in the number of copies of large DNA sequences," abbreviated as CNV) of two to 13 functional copies of a single CYP2D6 gene, increasing the rate of metabolism (Pierce 2012; PharmGKB 2012). This is detrimental through two separate mechanisms: more NAPQI is produced due to the higher metabolic rates, and the patient receives less pain relief, prompting them to take more acetaminophen and possibly overdose. Together, the three harmful phenotypes represent slightly greater than half the general population: PMs represent 10 % of the population, IMs represent 35%, and UMs are estimated to represent 7%. These percentages also vary between ethnic

populations. Asians, Pacific Islanders, Africans, and African-Americans have higher percentages of PM and IM alleles than Europeans and other Caucasians (Aulinskas 2010). CYP2D6 polymorphisms have also been implicated in adverse drug reactions (ADRs) to codeine (Brousseau et al. 2007).

SNP variation is also found in the genes encoding UDP-glucuronsyltransferases (UGTs), which are responsible for conjugating acetaminophen metabolites to glucuronide in the glucuronidation pathway (See *Figure 3*). A SNP in the promoter region of the gene that encodes UGT1A1 reduces promoter activity by 70%, thereby reducing the amount of UGT enzymes that are produced. Other SNPs located directly in the coding region of the gene have also been identified. One of these SNPs "results in reduced activity against phenolic compounds such as acetaminophen, salicylates and beta-blockers." Other SNPs cause a higher rate of glucuronidation (Flaherty 2007). Again, reduced amounts of enzyme are harmful because more acetaminophen must be diverted to harmful metabolic pathways, whereas higher rates of glucuronidation cause patients to experience less pain relief, resorting to more acetaminophen ingestion.

A possible solution to this problem of differing responses to acetaminophen lies in pharmacogenetics, the newly emerging branch of pharmacology in which genetic variation is correlated with a drug's efficacy or toxicity (Desnick). Between 1998-2005, the FDA recalled 19 drugs due to serious adverse drug reactions (SADRs), including hepatotoxicity, with genetic variation implicated as the cause (Giacomini et al. 2007; Need et al. 2005) (See *Figure 9*). Most of these drugs were approved much more recently than acetaminophen, which was grandfathered in by the FDA in 1968. In addition to the fact that several safer OTC alternatives to acetaminophen are readily available, this may be the single most convincing reason why

acetaminophen would not be approved by the FDA today, and it will be discussed later in *Future applications of pharmacogenetics to FDA regulation.*

However, future advances in pharmacogenetics could reduce the risk of SADRs to marketed drugs by allowing physicians to personalize drug regimens to their patients' genetic predispositions (Giacomini et al. 2007; Flaherty 2007). Unfortunately, the abundance of SNPs in each CYP enzyme keeps predisposition to acetaminophen overdose from being clear-cut; rather, it is on a gradient scale. There will be no "litmus test" for SADRs; these tests will require interpretation. Perhaps genetic tests could screen for PM, IM, and UM alleles in genes for CYP2D6 enzymes rather than trying to analyze every SNP in every CYP enzyme involved in acetaminophen metabolism. Furthermore, "interactions between genetic and nongenetic risk factors are unavoidable in many SADRs" and false positives may muddy test results (Giacomini et al. 2007). Additionally, genetic predisposition to acetaminophen overdose is far less extreme than other genetic diseases which are tested for at birth are much more extreme, such as Tay-Sachs disease, which causes untreatable deterioration of mental and physical abilities and death within the first year of life. However, genotyping people for hundreds of thousands or millions of SNPs is now so quick and inexpensive that it may be worth the lives of potential acetaminophen overdose victims anyway (Pierce 2012). For example, 23andMe is one of the many companies that offers personal genetic sequencing. Using only a small saliva sample, 23andMe's Personal Genome Service® will analyze one million SNPs in each customer's genome for only $99 (23andMe, Inc. 2012). Insurance companies and healthcare providers should be able to recognize that the cost of a $99 test is far less than the cost of a liver transplant or even several days spent in the hospital due to *Stage II* or *Stage III* acetaminophen overdose.

The acetaminophen overdose antidote

As stated previously, liver damage is caused by the depletion of glutathione (GSH), a natural antioxidant in the liver, by NAPQI. Accordingly, the antidote to acetaminophen overdose is a molecule that helps the body synthesize more protective GSH. Originally, the sulfur-containing amino acids methionine and cysteamine were used to try to restore GSH concentration (Heard 2008). Although these medications increased survival rates, the side effects, described as "flushing, vomiting, and misery" prompted researchers to find a better treatment (Heard 2008).

It is now known that GSH is naturally synthesized from the amino acids cysteine, glutamate, and glycine (Heard 2008). Glutamate and glycine are naturally abundant in liver cells, but cysteine is a limiting factor because it is not present in such high concentrations (Heard 2008). Unfortunately, cysteine cannot be administered as the antidote because it is not easily absorbed by the body (Heard 2008). Therefore, the antidote is N-acetylcysteine (NAC), which is quickly hydrolyzed to cysteine in the liver and then used to synthesize more GSH (Heard 2008; Saito et al. 2010). NAC was first used as the antidote to acetaminophen overdose in the late 1970's (Heard 2008).

One problem with this antidote is that its protective ability still remains unclear to scientists and medical professionals. In 2008, Kennon J. Heard, M.D. stated in a review of acetylcysteine use in acetaminophen poisoning, published in *The New England Journal of Medicine*,

> [Large clinical trials assessing the use of acetylcysteine] have not been performed. For example, there are no systematic studies evaluating the usefulness of acetylcysteine for patients who have hepatic injury...Nonetheless, the efficacy and apparent safety of this agent, as demonstrated in...two small studies, have led to widespread use of acetylcysteine therapy in almost all cases of acetaminophen-induced liver injury. A 2006 Cochrane review of the available data concluded that

> acetylcysteine "should be given to patients with overdose" but acknowledged that the quality of the evidence is limited. (p 288)

A 2010 study at the University of Kansas Medical Center attempted to clarify whether administration of NAC at later times (past 48 hours after ingestion) would still have a protective effect on patients' liver cells and whether GSH itself could be a better antidote to overdose. The researchers overdosed mice with acetaminophen and, ninety minutes later, treated some with GSH and some with NAC. The researchers found that the control group that had simply received an acetaminophen overdose had experienced severe liver injury, peroxynitrite (a highly damaging molecule that is due to oxidative stress) formation, and DNA fragmentation. Both treatments had hindered this damage in the other two test groups, but GSH itself was actually found to be more effective in preventing liver injury. Increasing the dose of NAC was found to have a similar effect as the original dose of GSH. The researchers also concluded that even late-stage application of either antidote prevented further liver injury (Saito et al. 2010).

However, the conventional wisdom is that the NAC antidote is most effective when administered before severe liver injury has occurred. Sources vary, citing between eight and 48 hours after ingestion as the best time of administration (Saito et al. 2010). Therefore, the antidote is most useful when cases of accidental ingestion, such as a young child drinking all of the Very Berry Children's Tylenol in the medicine cabinet because he or she likes the taste, are detected soon after ingestion occurs. Another such case could be when a patient has already been admitted to a hospital for an underlying disease or injury and too much acetaminophen is delivered. If someone other than the administering nurse or doctor checks the patient's chart, the antidote can be administered before it is too late.

The four stages of acetaminophen overdose

Dividing acetaminophen-induced ALF into four distinct stages is useful "because each stage has a different prognosis and is managed differently" (Heard 2008). In other words, identifying the stage of overdose is useful in determining whether damage can be reversed, and whether the antidote to acetaminophen overdose can be effectively administered. One of the reasons why acetaminophen overdose is so dangerous is that although early recognition and treatment of poisoned patients is essential to survival, the signs of overdose often cannot be observed until it is too late for any corrective medication to be administered. The course of acute acetaminophen toxicity is clinically divided into four stages: preclinical toxic effects, hepatic injury, hepatic failure, and recovery (Heard 2008). *Stage I* toxicity refers to the period of time after dosage when damage to the liver has not yet occurred. Patients in this stage may be asymptomatic, or may show clinical signs including nausea, vomiting, malaise (general feelings of discomfort), pallor (paleness of the skin), and diaphoresis (excessive sweating) (Goldfrank and Flomenbaum 2006). Unfortunately, some of these symptoms, especially malaise and diaphoresis (similar to a fever breaking) may mimic the symptoms for which the patient originally ingested acetaminophen. In fact, *Goldfrank's Toxicologic Emergencies,* a guide for emergency physicians, states, "These clinical findings should never be attributed to acetaminophen alone without thorough evaluation of other possible causes" (Goldfrank and Flomenbaum 2006). In extreme cases of "massive overdose," however, patients may show none of these symptoms, but will exhibit decreased levels of consciousness or metabolic acidosis, a condition in which too much acid is present in body fluids (Goldfrank and Flomenbaum 2006). In all *Stage I* patients, serum acetaminophen concentration of acetaminophen can be measured four to 24 hours after ingestion. If the serum concentration falls above a "possible toxicity" line

on a chart called the Rumack-Matthew Nomogram, first published in 1975, most US Poison Control centers will recommend treatment with the antidote (See *Figure 4*) (Heard 2008).

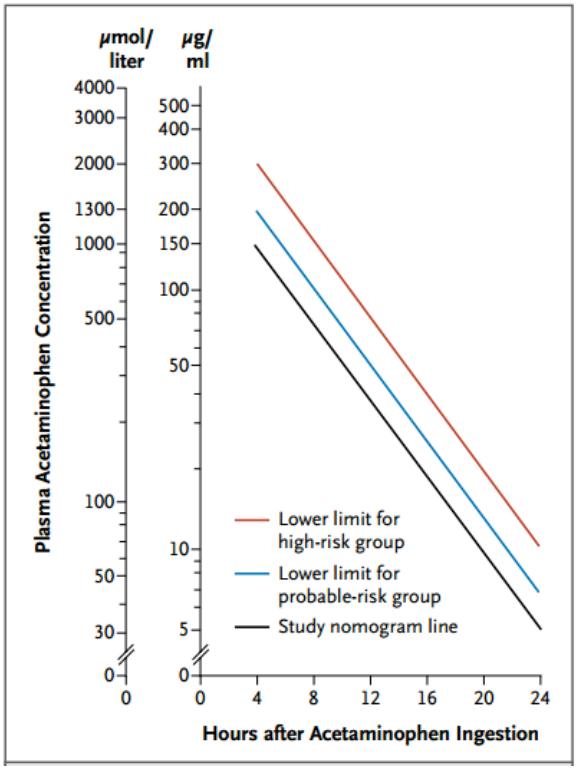

Figure 4: The Rumack-Matthew Nomogram, developed to estimate the likelihood of acute hepatic injury due to acetaminophen toxicity (Heard 2008).

The onset of liver injury marks the beginning of *Stage II* toxicity, which most often occurs within 24 hours of ingestion and universally occurs within 36 hours of ingestion in every patient (Goldfrank and Flomenbaum 2006). This stage of injury can be detected through higher levels of alanine amino-transferase enzymes, which are frantically trying to replenish glutathione reserves in the liver to detoxify NAPQI. This is most likely the same hepatic enzyme discovered in elevated levels during the autopsy of River Moore. Generally, patients are hospitalized for treatment if they have reached *Stage II* toxicity (Heard 2008).

Stage III is defined as "the maximal time of hepatotoxicity" in the patient and occurs between 72 and 96 hours after ingestion. Renal and kidney problems may also occur. Fatalities

due to acetaminophen overdose usually occur within three to five days after an acute overdose. Death is due to complications of multiorgan failure which include: hemorrhage, the profuse discharge of blood from the blood vessels; acute respiratory distress syndrome, which prevents oxygenation of the blood; sepsis, also known as blood poisoning, in which the bloodstream is infected with copious amounts of bacteria; and cerebral edema, excess accumulation of fluids in the brain (Goldfrank and Flomenbaum 2006). Patients who present with *Stage III* hepatic failure have a 20 to 40% chance of mortality (Heard 2008).

Stage IV, defined as the recovery phase, is only reached by patients who survive *Stage III* due to administration of the overdose antidote. Hepatic regeneration is fully achieved in survivors, and there is no indication of chronic hepatic dysfunction after recovery. Recovery may take as little as five to seven days or much longer in patients who undergo massive overdose, and, although acetaminophen-induced damage does not seem to be chronic, after an acute episode "histological abnormalities may persist for months" (Goldfrank and Flomenbaum 2006). It is also important to note that, in cases of liver failure, liver transplant is far from guaranteed. According to the United Network for Organ Sharing (UNOS), there are currently over 72,000 active candidates on the waiting list for a liver transplant in the United States alone (UNOS 2012). Moreover, the 2006 median waiting time in the United States was 321 days, which is acceptable for patients with chronic illnesses but greatly exceeds the remaining lifespan of patients suffering from acute acetaminophen overdose (Columbia University Department of Surgery 2012).

The Widespread Occurrence of Acetaminophen-Related Overdoses

Stage I acetaminophen overdose is far more common than the average acetaminophen user may expect, leading to over 100,000 calls to United States Poison Control Centers per year,

greater than that of any other OTC or prescription drug in use today. Every year, an estimated 56,000 visits to the emergency room and 2,600 hospitalizations are attributed to acetaminophen toxicity, leading to 458 deaths that are correlated with *Stage III* of acetaminophen overdose (Lee 2004). These statistics have been steadily increasing since acetaminophen's rise to popularity in the mid-1970's, and without an intervention, this phenomenon is likely to continue on an upward trajectory (Hawton et al. 1996).

The majority of acetaminophen-related emergency department visits are due to ingestion of less than or equal to ten pills (See *Figure 5*), revealing how extremely risky four extra doses of acetaminophen may be (Budnitz 2009). Furthermore, the egregiously large number of hospital admissions due to acetaminophen use highlights the intrinsically dangerous nature of the drug even when ingested according to its recommended dosage. Compounding the issue is the fact that no consensus exists over what is a safe level to consume. As stated previously, it is widely agreed upon that 7,000 milligrams/day causes severe liver damage in adults, but the level at which such damage actually begins to occur is predicted to be much lower. Levels as small as 2,000-4,000 milligrams have been implicated in approximately 10% of deaths related to acetaminophen. Considering that Extra Strength Tylenol capsules each contain 500 milligrams of active ingredient, as little as four capsules have the potential to cause terminal liver failure. This is particularly frightening upon the realization that this is only twice the recommended dosage, much less than one would use for the purposes of intentional self-harm (Beck 2009).

Considering the ease of accidental overdose, it seems that acetaminophen levels should be restricted, at least to the 325 milligram level found in regular strength Tylenol (Beck 2009). Unfortunately, the level of acetaminophen in OTC products has yet to be limited by governmental agencies such as the FDA, although restrictions have been imposed on the

acetaminophen levels in prescription drugs including but not limited to Vicodin and Percocet (Gardiner 2011). These restrictions will later be discussed in an analysis of the FDA's regulations on acetaminophen.

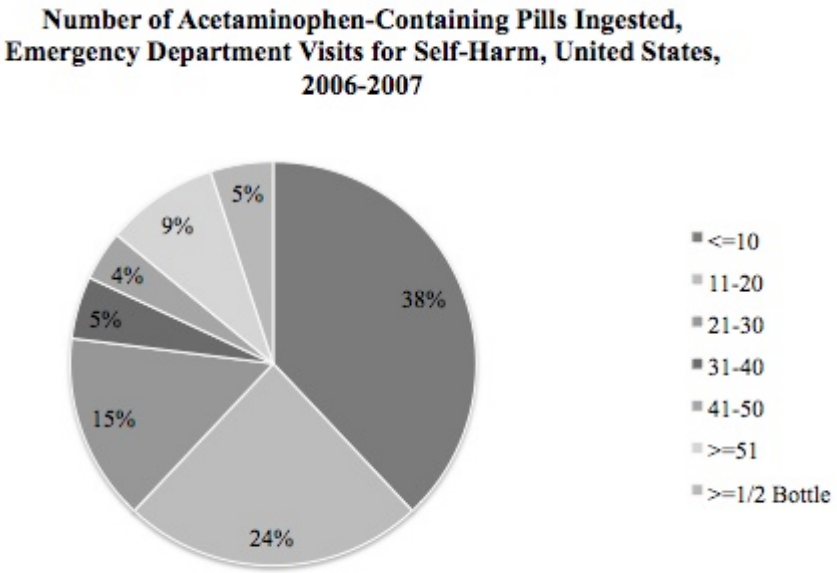

Figure 5: Estimates from the National Electronic Injury Surveillance System (NEISS); Based on 1,280 of 1,857 cases (69%) with pill/bottle count documented (Budnitz 2009).

The use of acetaminophen in self-harm

It is important to note the distinction between accidental and suicidal overdose, as Tylenol is much too often intentionally abused, especially in the UK, where acetaminophen has become the preferred substance of use in suicide attempts (Hawton et al. 1996). In 1976, before Tylenol had become popular, only 14.3% of all drug overdoses in Oxford, United Kingdom (UK) were caused by acetaminophen, but by 1993, acetaminophen overdose had come to account for 47.8% of all overdoses (Hawton and Fagg 1992). Similarly increasing rates of acetaminophen use in suicide have been noted in other countries including Denmark, Australia, and Scotland (Sheen et al. 2002).

This is relevant to our study of acetaminophen regulation because government food and drug agencies have phased out prescription painkiller medications that were heavily used in suicide attempts. For instance, in 2005, the popular analgesic and acetaminophen combination painkiller co-proxamol, used for "thousands of conditions such as back pain," was phased out by the Medicines and Healthcare products Regulatory Agency (MHRA), the European Union organization analogous to the FDA in the United States (BBC News 2005). This was because it was the "second most frequent means of suicide with prescribed drugs in England and Wales, accounting for up to 400 deaths each year" (BBC News 2005). BBC News, the first news organization that reported the phase-out, claimed that co-proxamol was more dangerous than acetaminophen. However, it seems that this claim may be unsubstantiated given that the suicide rates and number of deaths per year due solely to OTC acetaminophen are comparable to those of drugs like co-proxamol. This indicates a lack of consistency in FDA regulation of drugs commonly used in suicide attempt, which must be addressed immediately.

Studies have shown that acetaminophen's frequent use in self-harm can be attributed to its wide availability and its presence in many common OTC drugs that can be bought without a prescription, including Tylenol, Benadryl, Sudafed, Nyquil, and Dayquil (AHFS 2012). Furthermore, patients often choose to abuse acetaminophen because it is relatively inexpensive compared to other medications, furthering the ease of access argument. Interestingly, a 1995 study found that most individuals admitted to a hospital for acetaminophen overdose had chosen to do so with full knowledge of its potential to cause death. However, 53% of these attempted suicide victims inaccurately believed that an overdose would trigger unconsciousness, unaware that the fatal symptoms would not occur for several days after the overdose (Hawton et al. 1995). Had patients been aware of the two to three day delay in symptom presentation, they would not

have used it in attempt of suicide, opting for other methods that would have been quicker and more predictable (Gazzard et al. 1976). Thus, educating the public about the unpleasant reality of acetaminophen overdose may help to combat its frequent abuse.

The role of the media in acetaminophen overdose

The media could potentially save the lives of many would-be victims of acetaminophen through education. In a recent incident, an individual who was exposed to television coverage of acetaminophen-related suicide was able to use their subsequent awareness of the dangers of overdose to convince a friend that had taken a significant dose of Tylenol to seek treatment. Without having been exposed to this information, the friend of the overdose victim would not have been likely to intervene. Furthermore, the victim would probably not have received the Tylenol antidote and may have ended up developing complete liver failure. Thus, the media acts as a means of dissemination of important public health information and we would advise that it continues to perform this vital function within the context of acetaminophen-related overdose (Gunnell 1994).

Sadly, however, the media actually plays a large role in acetaminophen's rampant misuse. Media coverage of suicide, including both factual accounts in the news and fictional narratives in television dramas, is correlated with increased overall suicide rates, especially fueling instances of self-poisoning with the particular drug portrayed (Gunnell 1994). For example, a week after airing an episode of the UK hospital drama, "Casualty," in which an acetaminophen overdose was depicted, rates of attempted suicide increased by 17%, with 20% of those interviewed stating that the show had influenced them to purposefully overdose. Furthermore, 17% of patients reported that the broadcast had an effect on what drug they chose to use, leading them to select acetaminophen as their method of self-harm (Hawton et al. 1999).

Celebrity overdoses have also brought considerable attention to acetaminophen misuse. As one of the active ingredients in Vicodin, acetaminophen has played a role in many recent celebrity deaths including those of Brittany Murphy, DJ AM (Adam Goldstein), Heath Ledger, and Anna Nicole Smith (The Toronto Star 2012). Such frequent, highly visible overdoses provide proof of a normalization of deviance in which acetaminophen abuse has become so entrenched in popular culture that many choose to overlook the gruesome side of overdose in favor of the notion of a supposedly glamorous and easy way out. A recent study has even proven that celebrity overdose is independently associated with suicidal ideation, refuting the widely held assumption that celebrity overdose only affects those that are already vulnerable to suicide (Fu and Yip 2007). Thus, highly publicized overdoses can trigger suicide in anyone, regardless of the existence of predetermined conditions such as depression or other psychological disorders.

The role of the media in portraying acetaminophen overdose is highly controversial, although if carefully used, may be vital in preventing both accidental and suicidal overingestion through educational programs that promote awareness. It is advisable that the media uses caution in its presentation of acetaminophen-related suicide, making sure to provide the most accurate information possible so that viewers are well-informed of the dangers they may be putting themselves in if they choose to use the drug (O'Connor et al. 1999).

The high frequency of accidental overdose

Although about 50% of acetaminophen poisoning is intentional and suicidal in nature, a significant proportion of poisonings are accidental. Approximately 10% of poisonings are found in young children under the age of ten (See *Figure 6*). Overdoses in victims under five-years-old are somewhat obviously almost entirely unintentional, as children may inadvertently ingest acetaminophen products that they mistake as candy (Goepp 1996). A small percentage of

overdoses can be attributed to administration of an incorrect dosage either by parents, guardians, or the children themselves, although this occurs very infrequently because most parents are cautious against administering excess acetaminophen to their children, although they cannot always be certain due to the possibility of products containing higher-than-normal levels of active ingredient (Sheen et al. 2002). One study found that up to 30% of U.S. hospitalizations for acetaminophen overdose were due to accidental overdose (Schiodt et al. 1997), rivaling the 22% estimate comprising unsupervised child ingestions and other unintentional overdoses suggested by the FDA (See *Figure 6*). Regardless of which statistics are more accurate, accidental overdose is quite obviously prevalent enough to warrant substantial concern.

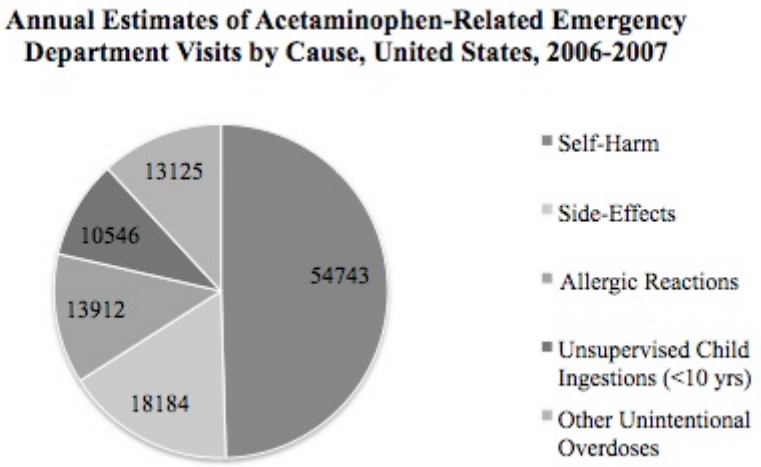

Figure 6: Estimates from the National Electronic Injury Surveillance System (NEISS); Based on 3,720 cases reported (Budnitz 2009).

Furthermore, it is often very difficult to distinguish accidental cases from those involving suicidal intent, leading us to believe that actual percentages of accidental overdose are probably much higher than reported. For example, coverage of the cases of Jennifer Needham and Emma Louise Payne are both somewhat unclear (See *Figure 7*), indicating that "no clear evidence of suicidal intent" exists without explicitly refuting the possibility of accidental overdose (The

Washington Post 1998, South Wales Echo 2011). Other cases much more clearly reveal the accidental nature of acetaminophen overdose, whether through long-term use of slightly higher levels than recommended, as in the case of Desiree Phillips (Collins 2012) or through excess administration by hospital staff, as in Danielle Welsh and Cynthia Shearer's unfortunate deaths (McCaffrey 2012, McDonald 2011). It is necessary to keep in mind that this analysis does not even begin to address the hundreds of thousands of accidental and intentional overdoses every year that are related to prescription medications containing acetaminophen, including Vicodin, Percocet, and Tylenol with codeine (Gardiner 2011).

Ironically, acetaminophen is included in prescription opioids with the intent of deterring patients from abusing them. Liver damage from acetaminophen is much harder to treat than damage arising from the opioid, resulting in a product that is actually much more dangerous to the user than the opioid alone. Although the addition of acetaminophen to prescription combination drugs has the potential to prevent overdose, this will not occur until awareness of the inclusion of acetaminophen in these products is more widespread (Szalavitz 2011).

Name	Drug	Date of Death	Age of Death	Cause of Death	Country
River Moore	Very Berry Children's Tylenol	July 22, 2010	2	Liver Failure	U.S.
Emma Louise Payne	Acetaminophen Pills	August 4, 2011	35	Liver Failure, Swelling of the brain	U.K.
Desiree Phillips	Acetaminophen Pills	August 2011	20	Liver Failure	U.K.
Cynthia Shearer	Acetaminophen Intravenous	April 12, 2011	68	Multi-organ failure	U.K.
Danielle Welsh	Acetaminophen Intravenous	June 18, 2008	19	Liver failure	U.K.
Jennifer Needham	Tylenol	Feb 22, 1998	19	Liver failure	U.S.

Figure 7: Acetaminophen overdose instances in the news, sampled from LexisNexis Academic (Sell 2012; South Wales Echo 2011; Collins 2012; McCaffrey 2012; McDonald 2011; The Washington Post 1998).

Recalls of acetaminophen-containing products

A number of recalls of OTC products containing acetaminophen have been conducted by the McNeil Company in recent years, revealing issues with regulation that hint at a general lack of concern within the company (The Associated Press 2012). In April 2010, Infant's and Children's Tylenol products were removed from drugstore shelves due to a failure to meet quality standards. Reports from McNeil indicated that the lots recalled might have contained elevated levels of acetaminophen (See *Figure 8*), which seems to have been connected with River Moore's death occurring soon thereafter (Sell 2012; McNeil Consumer Healthcare 2010a). Many recent recalls of Tylenol, Benadryl, and Sudafed products were caused by contamination with trace amounts of 2,4,6-tribromoanisole (See *Figure 8*), a chemical that produces a musty, moldy odor and may cause nausea upon ingestion (McNeil Consumer Healthcare 2011a,b). Although the inclusion of this chemical has no effect on the delivery of the active ingredient, it illustrates the type of careless culture that allowed other, more dangerous mistakes and ensuing recalls to occur. Another recent report cited excess levels of chlorpheniramine ammonio acetate (CAA), a compound normally found in Tylenol, as a reason for recall (See *Figure 8*). CAA is formed from the combination of chlorpheniramine maleate, which prevents runny nose and sneezing, and sodium starch glycolate, which allows pills to break down and release the active ingredient(s) (FOX News 2011). Thus, products with a higher than normal level of CAA may be metabolized more quickly, leading individuals to take Tylenol dosages more frequently in order to receive the same relief that a non-contaminated batch would offer. Both the August 15, 2010 and April 30, 2010 incidents, then, may have been directly involved in accidental overdoses. All

of these instances reveal a normalization of deviance within the McNeil Company that had serious consequences, namely liver failure and death, for its consumers.

Product	Reason for Recall	Date Recalled
Tylenol	Heightened Concentration of Active Ingredient	April 30, 2010
	2,4,6-Tribromoanisole	December 2009
		January 15, 2010
		October 18, 2010
		March 29, 2011
		June 28, 2011
	Chlorpheniramine Ammonio Acetate	August 15, 2011
Benadryl	2,4,6-Tribromoanisole	June 15, 2010
		July 8, 2010
		March 29, 2011
Sudafed	2,4,6-Tribromoanisole	March 29, 2011

Figure 8: Recent recalls of common OTC products containing acetaminophen (McNeil Consumer Healthcare 2012).

Alternatives to Acetaminophen

Acetaminophen's characteristic qualities include its abilities to act upon the central nervous system (CNS) and cross the blood-brain-barrier. The antipyretic and analgesic effects of acetaminophen are achieved through the inhibition of enzymes that are involved in prostaglandin E_2 (PGE_2) synthesis. Prostaglandins are not hormones, but are localized messenger molecules that cause pain. Acetaminophen directly inhibits the action of cyclooxygenase (COX)-2, an enzyme that synthesizes PGE_2. Additionally, acetaminophen binds to PGE synthase, a membrane protein that also generates PGE_2. Although it is still unclear in the scientific community, antipyretic activity may also be due to acetaminophen binding and inhibiting COX-3, another enzyme in the cyclooxygenase family. It is also unclear whether or not further analgesic activity of acetaminophen occurs by the indirect interference of serotonergic pathways, which are involved in mood control. Weak peripheral anti-inflammatory properties are due to limited inhibition of prostaglandin synthetase and COX enzymes in the peripheral nervous system

(PNS). This inhibition is weak because, while COX-2 is the primary synthesizer of prostaglandin in the CNS, COX-1 is more prevalent in the PNS, and it is not as highly affected by acetaminophen (Goldfrank and Flomenbaum 2006). The other class of analgesics, narcotics, also relieve pain by acting upon the central nervous system (MRODS 2003). In contrast, other OTC pain-relievers classified as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), which include aspirin (Bayer Aspirin, Ecotrin, Bufferin), ibuprofen (Advil, Motrin, Medipren, Nuprin, PediaCare Fever), naproxen sodium (Aleve, Anaprox, Midol, Naprelan), and ketoprofen (Orudis, Oruvail, Actron) act primarily upon the PNS, reducing inflammation more effectively. It is important for the public to realize that taking any of these painkillers only treats the symptoms and discomfort associated with any underlying disease by reducing the patient's ability to feel pain.

Narcotics

There are two main classes of analgesics: non-narcotics, such as acetaminophen and NSAIDS, and narcotics. Two classes also exist within the narcotics: opiates, which are derived entirely from the poppy plant, and opioids, which are composed of all-natural opiates and synthesized chemicals. Morphine, codeine, oxycodone, demerol, and vicodin are the most commonly used narcotic analgesics. All of these drugs are strictly regulated due to their highly addictive nature. Users can easily become physically and psychologically dependent on narcotics after just one use. When used excessively, dangerous side effects such as impairment of mental performance, drowsiness, dizziness, lethargy, blurred vision, convulsions, low blood pressure, slow heart beat, and death may result (MRODS 2003). Despite these risks, narcotics are frequently abused due to their ability to eliminate pain and create a peaceful, euphoric sensation for the user.

Morphine, the first narcotic analgesic, was extracted from the opium poppy in 1806, almost 100 years before the first non-narcotic analgesic, acetanilide (Maisto 2008). However, due to their addictive nature and dangerous side effects, narcotics cannot be used on an as-needed basis for mildly painful conditions. For this reason, the search for a safe and mild analgesic began, leading to the development of aspirin.

Aspirin

Aspirin was first derived from plants containing salicylate, a chemical that alleviates the symptoms of a variety of ailments such as fever and pain. By the end of the 1870s, salicylic acid was widely produced and used. Due to its anti-inflammatory properties, it was found to be particularly effective in treating arthritis. However, the chemical had an extremely negative effect on the stomach and was suspected to damage the heart. In 1899, the need for new antipyretic and analgesic alternatives was realized due to the "unsatisfactory nature of the drugs then available" (Andermann 1996).

Salicylic acid was altered and refined to form acetylsalicylic acid, the chemical name for aspirin. Aspirin was shown to have several advantages over salicylic acid; it no longer caused severe stomach irritation, cardiac depression, tinnitus (ringing or buzzing in the ears), or headache in normal doses. Changes made to the drug decreased side effects and increased its popularity. In the 1880s and 1890s, interest in methods to reduce fever increased dramatically. In the midst of the scarlet fever era, the negative effects of fever on the body were carefully studied. Aspirin's initial distribution coincided with this time period, and so the drug was initially used primarily as a fever reducer which caused its popularity to increase dramatically. However as the fever fad subsided, within the first five years after its release, aspirin was prescribed more for the relief of pain than it was for the relief of fever. (Andermann 1996). As the usage of aspirin

spread even farther, it became apparent that low doses of aspirin could prevent myocardial infarctions and strokes. Dr. Lawrence Craven was the first to report the antithrombotic effects of aspirin (Miner and Hoffhines 2007). This discovery led to the prescription of aspirin to patients with a predisposition for heart attacks in order to decrease their risk. While the drug has been refined and altered to reduce side effects, today high doses of aspirin can still cause stomach bleeding and renal failure. Due to these consequences, there is some speculation that aspirin would not be approved by the FDA today.

Ibuprofen

In the early 1950s, there was a search for new drugs for the treatment of rheumatoid arthritis (Adam 1992). As the mechanism of action for aspirin was researched, scientists attempted to create an alternative, drawing from the family of substituted phenylpropionic acids. While phenylpropionic acids were "originally rejected because of concerns about toxicity," clinical studies in animals suggested that they may be tolerated better than aspirin in the body (Adam 1992). In 1969, ibuprofen was launched as the first propionic. Ibuprofen proved to be effective not only for rheumatoid arthritis, but for an array of other mild to moderate painful conditions as well. Its spotless safety record allowed it to switch from a prescription to OTC in less than two decades. It has also proven to be "much safer than aspirin or acetaminophen in overdosage" (Adam 1992). From 1987 to 1996, the Toxic Exposure Surveillance System (TESS) "reported only 9 fatalities from 163,948 OTC ibuprofen exposures compared to 450 fatalities from 312,618 acetaminophen exposures, and 401 fatalities from 153,495 aspirin exposures" (FDA 2002b).

Naproxen sodium and ketoprofen

Naproxen sodium and ketoprofen are also a members of the propionic acid family. In a study published in 2011, naproxen sodium with associated with the least risk of stroke, while ibuprofen was associated with the highest risk, when compared to other NSAIDs including diclofenac, celecoxib, etoricoxib, rofecoxib and lumiracoxib (Trelle and Reichenbach 2011). While each of the other groups demonstrated an increased risk of cardiovascular death, naproxen sodium demonstrated a decrease when compared with the placebo group. While it may be safer in a cardiovascular context, naproxen sodium still carries its own risks. Like other NSAIDs, naproxen sodium and ketoprofen may cause ulcers, bleeding, or holes in the stomach or intestine without warning and may lead to death. Ketoprofen leads to elevated blood pressure and decreased coagulation. While acetaminophen clearly poses greater harm to the liver, hepatic side effects are also seen with use of ketoprofen.

Comparison of alternatives

Acetaminophen, aspirin, ibuprofen, naproxen, and ketoprofen all have the same purpose: to temporarily reduce fever and relieve minor aches and pains due to headache, muscular aches, arthritis, toothache, backache, the common cold, and menstrual cramps. Since they all have the same purpose, it is often difficult for the average person to distinguish between these drugs when choosing which to use. As NSAIDs, aspirin, ibuprofen, naproxen, and ketoprofen have similar risks and contraindications. Those who take anticoagulants, other NSAIDs, diuretics, drink alcohol regularly or have a history of stomach ulcers should not take NSAIDs. While the goal of each medication is the same, each drug works in a different way and poses a unique set of risks and side effects. One drug is not universally better than the rest. Rather, the effectiveness and

safety of common OTC antipyretic and analgesics is determined by the pre-existing conditions and proclivities of the user.

Out of all of the NSAIDs discussed, "ibuprofen has the most favorable GI safety profile" (FDA 2002a), meaning it has the least risk of causing stomach ulcers and bleeding. In a recent clinical study, it was also found to be either "comparable to or more effective than aspirin, acetaminophen, and various strengths of codeine-containing analgesics or other NSAIDs" (FDA 2002b). To determine the effect on pediatric fever, a study was done in which children were given ibuprofen, acetaminophen, and a combination of both drugs. It was shown that both treatments that contained ibuprofen reduced fever approximately 30 minutes sooner than acetaminophen (Drucker 2008). Children who received both drugs were afebrile for a longer period of time during the first 24 hours than those children who only took either acetaminophen or ibuprofen alone. No significant difference was shown in symptoms after the first 24 hours. This study clearly shows that acetaminophen is not the best option available as an antipyretic for children. Not only is the drug less effective, but it is also more detrimental to their health, causing problems with the liver and kidneys. While the combination of both drugs can alleviate fever faster, this benefit is only present during the first 24 hours of illness. Furthermore, the combination is even more hazardous than acetaminophen alone due to the metabolic interactions of both drugs in the body. For this reason, ibuprofen would be the best OTC antipyretic and analgesic option for those who are at risk for stomach problems. However, ibuprofen should not be taken if the user has high blood pressure or heart disease since long term usage of ibuprofen can exacerbate these conditions. Those at risk for heart attack or stroke should opt to use aspirin or naproxen sodium as opposed to acetaminophen, ibuprofen, or ketoprofen.

If used for a prolonged period of time, or at a higher dosage than recommended, aspirin can lead to renal failure. Children and teenagers who have flu-like symptoms or are recovering from the chicken pox should not take aspirin because it can lead to Reye's Syndrome, a potentially fatal condition that causes multisystem organ damage. However, aspirin is the suggested OTC antipyretic and analgesic for those who have a risk of stroke or heart attack because it reduces these risks. Naproxen sodium is another option for those with an inclination towards heart attack or stroke. On the other hand, acetaminophen, ibuprofen, or ketoprofen should be avoided at all costs in such situations.

The FDA: Then and Now

The current drug approval process

Today, the Food, Drug, and Cosmetic Act (FDCA) states that "no person shall introduce into interstate commerce any 'new drug,' unless that drug has an approved application by the FDA" (Abood 2006). Drug manufacturers must apply for and receive FDA approval for a new drug application (NDA), if the drug is not a generic of a drug currently on the market. The NDA process is extremely expensive and can take several years to complete due to the extensive amount of information required by the FDA before approving a new drug. Some information applicants must provide are full reports of experiments and investigations proving the drug's effectiveness and safety, the drug's composition and components, the methods, facilities, and controls used to manufacture, process, and package the drug, and also, the proposed labeling of the drug (Abood 2006). The drug should also be tested on a wide variety of ethnic demographics due to potential differences in drug response based on race.

To make the process easier for the approval of generic drugs, the FDA created a new form of NDA for called an abbreviated new drug application (ANDA) which allowed for faster

approval. This is because under an ANDA, proof of safety and efficiency was not required, but proof of acceptable manufacturing and controls and proof of bioequivalence must be provided. For generic drug equivalents marketed between 1938 through 1962, the FDA accepted ANDA applications with evidence of the drug's effectiveness and safety from the original manufacturer's studies rather than duplicating actual research for a NDA (Abood 2006). Since J&J was not required to re-evaluate the safety and effectiveness of acetaminophen and only complete an ANDA, extensive testing of acetaminophen was not conducted again, therefore, allowing this potentially harmful drug to stay on the market.

The history of the FDA

When acetaminophen was first created, there was no regulatory association to monitor if medications were safe and effective for humans. The first attempts to standardize drug regulation began in 1820 when eleven doctors set up the US Pharmacopeia, modeled after the British Pharmacopeia, and created the first list of standard drugs. One of the first laws created to regulate medicine was the Drug Importation Act, passed by Congress in 1848. This law required United States Customs Service to search and stop the entry of low quality or tainted drugs from being imported into the United States from overseas (FDA 2010a). It was not until 1905 that the American Medical Association (AMA) required drug companies to prove the effectiveness of their products before AMA or other journals would advertise the medication. In 1912, Congress passed the Sherley Amendment, which outlawed mislabeling medicines with fake medical claims meant to trick consumers. Finally, in 1930, the official name for the Food and Drug Administration (FDA) was modified from the previous title of Food, Drug, and Insecticide Administration (FDA 2010a).

The first incident which drastically changed the structure of the FDA was sulfanilamide poisoning. In 1937, Elixir Sulfanilamide, which contains the poisonous liquid, diethylene glycol, killed 107 people, many of whom were children. This dramatized the need to establish drug safety before marketing and pass stricter laws to regulate drugs. The sulfanilamide incident prompted Congress to pass the Federal Food, Drug, and Cosmetic Act (FDCA) of 1938, which required new drugs to be proven safe before they could be sold to consumers (FDA 2010a). This was the beginning of a new system of drug regulations. The FDA also required that dangerous drugs such as sulfanilamide be given under the direction of a medical expert, thus beginning the requirement for prescription-only medication. Then, in 1941, the FDA developed a set of guidelines called the Good Manufacturing Practices (GMP), which drastically changed manufacturing and quality controls after over 300 deaths resulted from the use of antibiotic sulfathiazole tablets, which were tainted with the sedative, phenobarbital (FDA 2010a). Both of these incidents are excellent examples of normalization of deviance because the FDA did not change their method of regulation until horrific incidents occurred. This forced the FDA to change their policies to prevent such disasters from occurring again, however, if the FDA had stricter policies earlier, these tragedies could have easily been avoided.

Nevertheless, it was not until 1962 that Congress required drug makers to prove that drug was effective and safe before the FDA would approve it for sale in the Kefauver-Harris Drug Amendments (FDA 2010a). These laws were mainly created as a response to severe birth defects of thousands of babies born in Western Europe due to Thalidomide, a relatively new sleeping pill. In 1968, the FDA formed the Drug Efficacy Study Implementation (DESI) to review the effectiveness of drugs sold from 1938 to 1962 (FDA 2010a). It was here that medication such as acetaminophen and aspirin that were “grandfathered” in were reviewed again for effectiveness

but were ultimately re-approved. The Over-the-Counter Drug Review began to enhance the safety, effectiveness, and appropriate labeling of medication, such as acetaminophen, sold without prescription (FDA 2010a).

One incident that dramatized package of medication was deaths caused by cyanide placed in Tylenol capsules. In response, Congress passed the Federal Anti-Tampering Act in 1983, making it a federal crime to tamper with packaged consumer products. In 1998, the FDA created the Drugs Facts Label so that all OTC products, including Tylenol and Aspirin, would have information in a standard format. Although these Drug Facts labels were designed to allow the consumer to easily identify information, there were still discrepancies between different products (FDA 2010a). For example, unintentional acetaminophen-related overdoses continued because manufactures interchanged between using "acetaminophen" and "APAP," confusing consumers who unknowingly took multiple products containing acetaminophen.

More recently, the FDA formed the Drug Safety Board in 2005. This Board, which consisted of FDA staff as well as representatives from the National Institute of Health (NIH) and Veterans Administration (VA), advises the FDA and the Center for Drug Evaluation and Research (CDER) on drug safety issues. They also work with the FDA to to share safety information with health professionals and patients (FDA 2010a). Since education is one of the best ways to reduce misuse and unintentional injury while using both prescription and OTC medication, the formation of such a review board and education program will help increase drug safety.

Acetaminophen regulation by the FDA

Since its approval in 1955, the regulation of acetaminophen by the FDA has drastically changed in both prescription and OTC products, including labeling format changes as well as

increased warning labels. The FDA claims that it was not until the late 1990s that research began to prove a correlation between unintentional overdose of acetaminophen and ALF. In response to such concerns, the FDA began taking steps to reduce acetaminophen-related liver injury. In 1998, the FDA finalized a regulation requiring alcohol warnings be added to OTC packages of acetaminophen. This warning advised consumers who drank 3 or more alcoholic drinks a day to ask their doctor whether they should take acetaminophen or other pain relievers (FDA 2011). Later, in 2002, the FDA held a public advisory committee meeting focused on unintentional liver injury related to the use of OTC acetaminophen. The committee recommended inclusion of a liver toxicity warning as well as distinctive labeling on OTC medication so that acetaminophen could be more easily identified as the active ingredient. The committee also stressed the need for the FDA and manufacturers to educate consumers and health professionals about the risk of liver injury due to acetaminophen (FDA 2011).

This prompted the FDA to launch a public education campaign in early 2004. The goal of the campaign was to help consumers understand how to use both NSAIDs and acetaminophen medication more safely. Also in 2004, the FDA sent letters to all US State Boards of Pharmacy asking that they add new labels to prescription products containing acetaminophen. These new labels would use the term acetaminophen instead of APAP, warn patients about taking other medication with acetaminophen, and instruct patients not to exceed the maximum daily dosage and to avoid drinking alcohol during prescription use (FDA 2011). However, as of February 2008, the National Association of Boards of Pharmacy reported that no states had implemented regulations related to the request. In 2007, the FDA's Center for Drug Evaluation and Research organized a multidisciplinary working group to review safety issues related to acetaminophen products. This led the FDA to issue a final regulation for the labeling of OTC products

containing acetaminophen, including an alcohol warning, severe liver damage warning, and "consult a doctor before taking acetaminophen" warning in April 2009 (FDA 2011).

Future applications of pharmacogenetics in FDA regulation

Integration of pharmacogenetics in FDA regulation would constitute FDA requirement of more detailed genetic data during the drug evaluation process and more complex prescribing information (Shah 2005). As described previously, future applications of pharmacogenetics could consist of genetic testing of patients seeking prescription pain medications for short-term ailments, genetic testing of patients suffering from chronic pain, or even genetic testing at birth. Ideally, pain treatment could be tailored to each specific patient's genetic predisposition to acetaminophen; if it is found that a patient is a CYP2D6 UM, for instance, the doctor can decide to "use another drug, adjust the dose or monitor the patient more closely" (Giacomini 2007).

Some existing regulatory guidelines "recommend exploration of the role of genetic factors when investigating a drug for its pharmacokinetics, pharmacodynamics, dose-response relationship, and drug interaction potential." For instance, in March 2005, the FDA issued a final guidance notice about a "voluntary submission of genomic data." This guidance encourages new drug developers to collect pharmacogenetic information during preliminary drug trials and submit this data to expert regulatory groups for discussion without any concerns about the adverse impact of sharing this data with developers. This concept of "safe harbor" implies that all pharmacogenetic data disclosed to regulatory groups will not be able to be used for initiating any preventive regulatory actions. Rather, this encourages discussions between the developers and the regulators to exam pharmacogenetic data from a wide range of drug development programs. This should then facilitate logical applications of pharmacogenetics to subsequent drug development and, ultimately, to clinical therapeutics (Shah 2005).

Drug	Indicated Use	Withdrawal Date, Country	Reason for Withdrawal	Genes Related to Mutation
Alpidem	Anxiety disorder	1994, France	Hepatotoxicity	BZRP, CYP1A1, CYP1A2
Astemizole	Allergies	1999, US	QT interval prolongation and TdP	CYP2J2, KCNH2, KCNQ1, KCNE1, KCNE2, KCNE3
Bendazac	Cataract treatment	1993, Spain	Hepatotoxicity	
Cerivastatin (Baycol, Lipobay)	Hypercholesterolemia	2001, Worldwide	Rhabdomyolysis	CYP2C8
Chlormezanone (Trancopal)	Anxiety disorder	1996, Worldwide	Hepatotoxicity	HLA-B
Dexfenfluramine (Pondimin)	Obesity	1997, Worldwide	Risk of heart valve abnormalities and pulmonary hypertension	CYP2D6, BMPR2, HTR2B
Dilevalol	Hypertension	1990, Worldwide	Hepatotoxicity	UGT genes
Nefazodone (Dutonin, Serzone, Nefader)	Depression	2003, Canada Europe	Hepatotoxicity	
Pemoline (Cylert)	ADHA	1997, Canada Europe	Hepatotoxicity	
Terodiline	Urinary incontinence	1992, Worldwide	TdP	CYP2C19
Troglitazone (Rezulin)	Glycemic control	1997, UK	Hepatotoxicity	CYP2C19, GSTT1, GSTM1
Trovafloxacin (Trovan)	Bacterial infections	1999, Worldwide	Hepatotoxicity	

Figure 9: Drugs withdrawn from major markets due to hepatotoxicity or variation in CYP enzyme activity, sampled from "Drugs withdrawn from major markets since 1990" (Need et al. 2005).

Above is a table of a small fraction of drugs withdrawn worldwide between 1990 and 2005 due to SADRs such as hepatotoxicity. The last column in the table indicates candidate genes for future investigation that have been implicated in the SADRs that resulted after patients were treated with each drug (Need et al. 2005). Although these drugs were not all withdrawn by the FDA, the data does indicate that SADRs are serious concerns during the drug evaluation process. According to a commentary in *Nature* entitled, "When good drugs go bad," 19 drugs have been withdrawn from the US market since 1998 due to "unpredictable patient fatalities." Additionally, the commentary states, "For life threatening cancers, potentially fatal SADRs will

be tolerated, but for an antihistamine, even the slightest risk of an SADR is not acceptable" (Giancomini et al. 2007). Although acetaminophen overdose is hardly unpredictable anymore, why should it be considered any differently from an antihistamine?

This data indicates that if acetaminophen had not been passed through during FDA re-evaluations in 1968, it would not be approved by the FDA today. However, these drugs, and acetaminophen, may be reconsidered in the future due to advances in pharmacogenetics. For drugs like these to be considered on an individualized basis, significant advances need to be made in the field. Predictive genetic tests for SADRs need to be fully developed and standardized. Additionally, a global pharmacogenetics network needs to be established so that all ethnicities, and all alleles, are considered. Some problems with SADR predisposition described in "When good drugs go bad" include the fact that, in most cases, little to no information about the underlying biological mechanisms is available and that the numbers of SADR cases are "too small for adequate genetic analysis" (Giacomini 2007). Accordingly, acetaminophen is the perfect drug for SADR testing because we *do* have information about the biological mechanisms of metabolism and the number of overdose cases that can be analyzed is very large. It is important to remember, however, that acetaminophen overdose is not solely due to genetic predisposition, and that many of these cases are simply due to over-ingestion of acetaminophen.

Further recommendations for reducing acetaminophen overdose

There are several options for reducing unintentional acetaminophen-related liver injury. One potential option is to reduce the current individual dosage or implement restrictions for current maximum daily dosage sizes. Since there is little difference between the maximum daily dose and the potentially harmful dose, acetaminophen has a very narrow safety margin. If the recommended daily dose of acetaminophen in OTC products such as Tylenol and Excedrin and

in prescription products such as Hydrocodone and Percocet is lowered, the likelihood of accidentally exceeding the safe dose will be drastically reduced. Creating packaging size limits for OTC acetaminophen products may also lower risk of liver injury (FDA 2011). Currently, acetaminophen-containing products can quite easily be purchased from a wide range of drug stores and pharmacies. These products, which come in tablet, capsule, or liquid form, often have packaging sizes that can contain up to hundreds of doses. By limiting the number of acetaminophen doses that can be contained in a single package and restricting the amount of acetaminophen that can be bought at one time, it would become more difficult to obtain large quantities of acetaminophen, and therefore, decrease both intentional and unintentional overdoses. Additionally, if tablets were packaged in blister containers instead of bottles, consumers could be more likely to keep track of their acetaminophen intake and thus ensure that they have not ingested excessive numbers of pills (FDA 2011).

Another way to lower acetaminophen related injury is to require "unit-of-use" packaging for prescription products. The phrase "unit-of-use" refers to the fact that since many products come to pharmacies and drug stores in bulk quantities, pharmacists are able to repackage the medication to accommodate the patient's individual needs. The newly proposed packaging system would require the product to come to the pharmacy ready for sale; therefore, the pharmacist will not have to repackage it. This will then provide the FDA the ability to standardize the information laid out on the prescription label, warnings, and description of active ingredients on the dispensing package itself. "Unit-of-use" packaging would reduce overdoses because the FDA-approved labeling information of the product would consistently remind the consumer of the risks associated with acetaminophen (FDA 2011).

A fourth option is to expand product warning information on prescription medication. Recently, the FDA issued new labeling regulations for OTC products that contain acetaminophen, but has yet to improve the labeling of prescription products containing acetaminophen combined with other drugs. Currently, there is no prominent warning on the prescription bottle about the risk of liver injury or any other patient directed information about the risks inherent in acetaminophen use. Today, many patients do not realize that the prescription medication they are taking contains acetaminophen, therefore, when they take an acetaminophen-containing OTC products, they are unintentionally putting themselves at risk for liver failure. This option would require that all prescription products have a standard set of regulations such as a standard warning about liver injury, a medication guide focusing on liver injury risk, as well as the full name "acetaminophen" written on pharmacy dispensed bottle rather than "APAP" or other misleading or confusing identifiers (FDA 2011). This will allow consumers to easily identify products with acetaminophen, and thus, reduce unintentional overdose with OTC and prescription acetaminophen products.

Another recommendation consists of regulating acetaminophen product purchases, similar to the way other restricted OTC substances are controlled. For instance, due to fears surrounding methamphetamine production, OTC products containing pseudoephedrine (PSE) do not require a prescription, however, consumers must ask a pharmacist for them. In all states, consumers must sign for the product, show identification to purchase it, and cannot purchase more than nine grams per 30 day period. Although acetaminophen cannot be made into an addictive drug, purchases of acetaminophen-containing products could be just as tightly controlled to prevent overdose and to alert consumers of the possible dangers of acetaminophen ingestion (FDA 2010b).

A more radical choice is to remove all combination OTC and prescription products that contain acetaminophen. Today, there are hundreds of different OTC and prescription products that contain acetaminophen along with other active ingredients. Since consumers are not always aware that acetaminophen is present in so many different combinations, the likelihood of unintentional overdose drastically increases. By eliminating these combination products, the risk of unknowingly duplicating doses by taking multiple OTC and prescription acetaminophen containing products will significantly be lowered (FDA 2011).

A final possible recommendation would specifically apply to liquid OTC products. These products should have a limit dosing formulation with a standard concentration of acetaminophen and a dosing device to administer the proper amount of medication. Liquid products, which are mostly used for treating children, are available in different concentrations for children of different ages. For example, liquid acetaminophen that is intended for use in infants is typically more concentrated than those for older children, allowing less liquid to be administered for proper dosages. This makes it possible to mistakenly overdose an older child if administering a liquid product intended for an infant. Also, current regulations do not require that a measuring device be included in the product package (FDA 2011). If there is one standard concentration and a measuring device, overdoses attributed to administering the wrong dose of different concentrations of medication and overdoses due to inaccurate measurement could be reduced.

Conclusion: Would the FDA Approve Acetaminophen Today?

Owing to the FDA's current stricter criteria for drug approval today, the considerable amounts of documented literature that have linked acetaminophen usage to liver failure, the presence of PM and UM genetic variation in the general population, and the high rates of both intentional and accidental acetaminophen overdose, we conclude that acetaminophen would not

be approved by the FDA today. However, we recognize that because acetaminophen is so deeply ingrained in our culture as a "go-to" fever and pain reducer and is supported by a multi-billion dollar pharmaceutical giant, the FDA would not be likely to re-evaluate its approval. Therefore, we have put together a set of recommendations for lowering acetaminophen-related liver injury.

One seemingly obvious option is to educate consumers of the detrimental side effects related to acetaminophen use. In one study conducted in the United Kingdom, patients admitted to the hospital with an accidental acetaminophen overdose were asked about factors that might have prevented them from taking too much of the medication. The survey found that "although 66% would still have used acetaminophen with the knowledge that it could cause death, only 35% would still have used it had they known that the harmful effects could be delayed for several days" (Sheen et al. 2002). By educating the public about the lethal consequences of acetaminophen, consumers would be less likely to unintentionally overdose by taking multiple medications containing acetaminophen.

The FDA has been expanding its existing educational program to reach both the public and healthcare professionals. To encourage safe practices of acetaminophen use, the campaign focuses on taking only the recommended dose of acetaminophen, avoiding mixing acetaminophen-containing products, and asking a doctor about taking acetaminophen products if one plans to consume alcohol or is already susceptible to liver disease. However, as shown by the large catalogue of documented unintentional overdoses even since this campaign began, a larger attempt clearly needs to be made. The public can also be educated about the antipyretic and analgesic alternatives to acetaminophen. Risk of liver and kidney damage can be dramatically reduced through use of ibuprofen instead of acetaminophen. Therefore, we

recommend that for the purposes of pain and fever relief, ibuprofen be the preferred choice of drug over acetaminophen.

Another important recommendation to reduce liver injury is to create a safer and more effective antidote and acetaminophen combination drug, which would have no effect on pain relief, but would replenish stores of glutathione in the liver as it was depleted by NAPQI. In the same study conducted in the UK, overdose patients said that "if an antidote were contained within the paracetamol tablet, 64% would not have taken the overdose" (Sheen et al. 2002). This is possibly due to the psychological stigma that this action would attach to the use of acetaminophen, as potential users would understand that if a drug must be administered with its antidote, it must be sufficiently dangerous. One combination methionine-acetaminophen combination tablet, Paradote, was released on the UK market in 1987 and is still currently available. However, this combination drug costs nearly six times that of generic acetaminophen. Even worse, a study showed that the dose of methionine actually needed to reduce liver damage would be considerably greater than the 800 milligrams of methionine included with 4,000 milligrams of acetaminophen in Paradote (Sheen et al. 2002). Finally, it is also notable that this combination tablet contains methionine, an antidote used before the 1970's, rather than the currently used acetaminophen antidote, NAC. Research efforts could be directed toward combining acetaminophen with NAC and reducing the cost of the new NAC-acetaminophen combination medication.

The final recommendation is to standardized labeling on all OTC and prescription acetaminophen-containing medication. Currently, all OTC products with acetaminophen have an alcohol warning, liver damage warning, and the ingredient name *acetaminophen* in bold or highlighted print; however, prescription products do not have the same labeling requirements.

These prescription products alternate between using the full name acetaminophen and the abbreviation APAP, which ultimately confuse consumers. By creating a standard labeling method, consumers will be more aware of OTC and prescription medication containing acetaminophen, and therefore reduce the occurrence of unintentional acetaminophen overdose and liver damage.

Frequent acetaminophen use and abuse clearly constitutes a "normalization of deviance," defined earlier as a failure of foresight that results from the continuous act of ignoring deep concerns while making formal risk assessments that dismiss signs of danger. It is apparent that US and UK consumers readily ignore the ease and tendency with which accidental overdose occurs, choosing to ingest extra doses of acetaminophen with the misconception that a widely available, FDA-approved drug could not possibly be so life-threatening. To the highly trained observer, acetaminophen seems to be ingested with the same regard as one would give to a daily multivitamin. In this regard, liver injury is thus wrongly assumed to be a concern of only the alcoholic and not of the Tylenol user.

Our ultimate goal in this paper is analyzing the ways in which unnecessary liver injury and death can be prevented. Unfortunately, the extremely high number of recent recalls of OTC acetaminophen-containing products reveals another culprit of normalization of deviance, Johnson & Johnson and its subsidiary, the McNeil Company. This has serious consequences, namely liver failure and death, for its consumers. This is not a mere point of contention, but is a notion so completely unacceptable that it must be addressed with great urgency. If J&J and the McNeil Company clean up their acts, in combination with increased education, labelling, and packaging changes by the FDA, acetaminophen may be able to be used in a much more safe and

predictable manner. In addition, if personalized medicine becomes a reality in the future, doctors may be able to prescribe acetaminophen to patients who are able to safely metabolize the drug.

On the other hand, more lives may be able to be saved if acetaminophen were outright removed from the market, but because the drug is so deeply entrenched in society today, we realize that this may not be a realistic option to pursue. Instead, we hope to make less drastic recommendations that, if enacted, would make it safer for individuals to use acetaminophen if they choose to do so. Once consumers, pharmaceutical companies, and government regulatory bodies become aware of the normalization of deviance accompanying society's use of acetaminophen, we may finally see a day when the risks involved in acetaminophen use is practically eliminated.

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Honor Pledge

I pledge on my honor that I have not given or received any unauthorized assistance on this assignment/examination.

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