Regulatory History: Elixir Sulfanilamide

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OVERVIEW
Elixir Sulfanilamide was an antibiotic drug product available in 1937. Its formulation caused more than 100 deaths in 15 states. Many of these deaths were children. This catastrophe increased public awareness of the potential dangers with drugs. Responding to a shocked nation, congress passed the 1938 Food, Drug, and Cosmetic Act, which significantly changed drug regulation in the United States. This act granted the US Food and Drug Administration more jurisdiction over drug products and revolutionized the current drug approval process. This paper provides a brief summary of Elixir Sulfanilamide and its subsequent regulatory ramifications. Today, despite the great noteriety of diethylene glycol (DEG) toxicity since 1937, instances of poisoning still occur (1-3).

SULFANILAMIDE
The sulfanilamide molecule (Figure 1) was discovered in coal-tar dyes being used in Germany in the early 1900s.

Sulfanilamide contains a sulfonamide moiety attached to aniline. The drug is more pharmacologically active in its protonated form. Its solubility is low, approximately 7.5 g/L at 25°C in water. This low solubility is an important physical property affecting formulation, processing, and pharmacology. Sulfanilamide’s toxic effects may include crystallization in the kidneys.

Sulfanilamide is the active metabolite from the drug sulfonamidochrysoidine. Prontosil, the first commercially available sulfa antibiotic in the 1930s, was a tablet product containing sulfonamidochrysoidine. After in vivo metabolism, sulfanilamide interferes with folic acid synthesis by inhibiting pteridine synthetase through competition with para-aminobenzoic acid as a substrate for the enzyme. Blocking this crucial step kills bacteria, successfully treating many major diseases such as malaria, tuberculosis, and leprosy, and leading to the “sulfa craze” of the 1930s. The basic chemistry of the sulfa drugs resulted in many new molecules. Even today, sulfa-based drugs like sulfamethoxazole and sulfadiazine are used to treat infection, while some other sulfas such as furosemide are used as diuretics (4-6).
DIETHYLENE GLYCOL

DEG is a widely-used industrial chemical and solvent. This substance can be found in products such as dyes, oils, lubricants, inks, glues, brake fluids, and other applications. It has also been used as an anti-freeze. DEG is an important molecular building block in organic synthesis. It is no longer allowed in foods or drugs, although trace amounts may be present as it is a byproduct of polyethylene glycol, a common food additive. Although colorless and odorless, DEG has a somewhat sweet taste. It is readily miscible in water and alcohol, contributing to its desired solvent properties. It appears frequently as an unwanted impurity in many different products. Although little data are available for humans, the lethal dose (LD₅₀) for mammals is between 2-25 g/kg (4). Ingesting even trace amounts can lead to gastrointestinal problems and altered mental status, while more lethal doses inevitably lead to metabolic acidosis, kidney failure, and dangerous neurological complications. These symptoms are quite similar to the toxic symptoms suffered by the victims of the 1937 sulfanilamide tragedy (7-8).

ELIXIR SULFANILAMIDE

Sulfanilamide was a very successful therapeutic agent in the 1930s. The groundbreaking anti-microbial of the era, sulfanilamide was marketed throughout the nation. Prior to the introduction of penicillin in the 1940s, sulfanilamide was the only effective antibiotic. Discovered accidentally, sulfanilamide was revolutionary in treating infectious disease.

A commercial need for a liquid formulation of sulfanilamide product for treatment of children was recognized. Formulation scientists at the S.E. Massengill Company determined that a formulation containing sulfanilamide, diethylene glycol, and raspberry flavor could be manufactured. Diethylene glycol served to dissolve the insoluble sulfanilamide, and also had a sweet taste. The company launched the product without any safety testing, not realizing diethylene glycol was quite toxic to humans. Safety testing of pharmaceuticals was not required at that time. Numerous batches were produced and distributed nationally. Reports of toxic symptoms and fatalities quickly surfaced. Many of the victims were children being treated for sore throats. These children suffered convulsions, pain, nausea, and kidney failure. One mother described her child as follows: “we can see her little body tossing to and fro and hear that little voice screaming with pain and it seems as though it would drive me insane. ... It is my plea that you will take steps to prevent such sales of drugs that will take little lives and leave such suffering behind and such a bleak outlook on the future as I have tonight (1).” Perhaps even more disconcerting than this mother’s plea is that the drug firm, S.E. Massengill Company, was a respected company (9). Patients trusted their medication because it came from an establishment with a stellar reputation. Upon learning of these poisonings, S.E. Massengill swiftly telegraphed its customers, but for many it was too late. When the last batch was finally recovered, more than 100 patients had died. This scandal served as a wake-up call. The time had come for proper regulation of drug safety.

REGULATORY LEGISLATION

Thus began legislation enacting the 1938 Food, Drug, and Cosmetic Act. Congress extended FDA’s powers to include regulation of drug safety, and required pharmaceutical manufacturers to include animal testing data. In a day and age requiring multiple phases of clinical trials, it is hard to imagine society without such safety precautions. Seventy years ago, however, it was a desperately necessary advancement. Prior to 1938, the safety requirements were marginal at best under the 1906 Pure Food and Drug Act. The 1906 act served only as a mandate for proper labeling and banning sale
of certain narcotics. The only real action FDA could take against any company was to confiscate an adulterated or misbranded substance. In fact, the only charge against S.E. Massengill according to federal law was mislabeling, as the product was a solution instead of an elixir. Even with more than 100 deaths, the current law did not hold the manufacturer responsible despite no animal testing and diethylene glycol toxicity being well known at that time. Both Congress and the American public realized the need for full evaluation of new drugs coming to the market, and not just cursory taste tests.

The 1938 law involved more stringent control of new drugs, demanding proof of safety before the drug could enter the market. The scope of the new law included homeopathic medicines and therapeutic devices as well. If the substance was in the Homeopathic Pharmacopoeia of the United States, it fell under the jurisdiction of FDA. Additionally, the Food, Drug, and Cosmetic Act authorized factory inspections to improve drug safety and enforce new policies. Not only was the 1938 Food, Drug, and Cosmetic Act the next step in improving public health and safety, but also it was essential in paving the way for the current drug approval process. This milestone act changed the way the US regulated drugs. Much of the current legislation is based on this one landmark event. Some even claim it is the reason the thalidomide tragedy did not reach the US. Despite this tragic calamity of the infamous elixir sulfanilamide poisonings, it was the push the country needed to create a better method for the drug approval process. One small event can make a big difference. All of this stemmed from the infamous elixir sulfanilamide (1-10).

CURRENT DIETHYLENE GLYCOL POISONINGS
Despite widespread knowledge and understanding of the 1937 Elixir Sulfanilamide incident, reports of diethylene glycol poisoning around the world still occur. DEG toxicity has been reported numerous times. Fraudulent substitution of DEG for glycerin has resulted in symptoms of toxicity and death. Even though DEG is not allowed in foods or drugs, its widespread use as an industrial chemical makes it available for illegal use by unscrupulous individuals.

REFERENCES

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