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Sulfanilamide Disaster FDA Consumer magazine June 1981 Issue

Taste of Raspberries, Taste of Death
The 1937 Elixir Sulfanilamide Incident

By the 1930s it was widely recognized that the Food and Drugs Act of 1906 was obsolete, but bitter disagreement arose as to what should replace it. By 1937 most of the arguments had been resolved but Congressional action was stalled. Then came a shocking development--the deaths of more than 100 people after using a drug that was clearly unsafe. The incident hastened final enactment in 1938 of the Federal Food, Drug, and Cosmetic Act, the statute that today remains the basis for FDA regulation of these products.

by Carol Ballentine

Nobody but Almighty God and I can know what I have been through these past few days. I have been familiar with death in the years since I received my M.D. from Tulane University School of Medicine with the rest of my class of 1911. Covington County has been my home. I have practiced here for years. Any doctor who has practiced more than a quarter of a century has seen his share of death.

"But to realize that six human beings, all of them my patients, one of them my best friend, are dead because they took medicine that I prescribed for them innocently, and to realize that that medicine which I had used for years in such cases suddenly had become a deadly poison in its newest and most modern form, as recommended by a great and reputable pharmaceutical firm in Tennessee: well, that realization has given me such days and nights of mental and spiritual agony as I did not believe a human being could undergo and survive. I have known hours when death for me would be a welcome relief from this agony." (Letter by Dr. A.S. Calhoun, October 22, 1937)

The medicine that killed Dr. Calhoun's patients was Elixir Sulfanilamide. During September and October 1937 this drug was responsible for the deaths of more than 100 people in 15 states, as far east as Virginia and as far west as California. The drug and the deaths led to the passage of the 1938 Food, Drug, and Cosmetic Act, which increased FDA's authority to regulate drugs.

Sulfanilamide, a drug used to treat streptococcal infections, had been shown to have dramatic curative effects and had been used safely for some time in tablet and powder form. In June 1937, however, a salesman for the S.E. Massengill Co., in Bristol, Tenn., reported a demand in the southern states for the drug in liquid form. The company's chief chemist and pharmacist, Harold Cole Watkins, experimented and found that sulfanilamide would dissolve in diethylene glycol. The company control lab tested the mixture for flavor, appearance, and fragrance and found it satisfactory. Immediately, the company compounded a quantity of the elixir and sent shipments--633 of them--all over the country.

The new formulation had not been tested for toxicity. At the time the food and drugs law did not require that safety studies be done on new drugs. Selling toxic drugs was, undoubtedly, bad for business and could damage a firm's reputation, but it was not illegal.

Because no pharmacological studies had been done on the new sulfanilamide preparation, Watkins failed to note one characteristic of the solution. Diethylene glycol, a chemical normally used as an antifreeze, is a deadly poison.

The first shipments were sent out in early September. On October 11, the American Medical Association (AMA) received reports from physicians in Tulsa, Okla., that an unfamiliar sulfanilamide compound was responsible for a number of deaths. The AMA asked for samples of the drug and then wired the Massengill Co., requesting the composition of the compound. The AMA laboratory isolated diethylene glycol as the toxic ingredient and immediately issued a warning, through newspapers and radio, that Elixir Sulfanilamide was toxic and deadly.

A New York physician learned of the deaths on the 14th and promptly notified Food and Drug Administration headquarters. An inspector from the agency's Kansas City Station confirmed that eight children and one adult had died and that all had taken a product labeled "Elixir Sulfanilamide, the S.E. Massengill Co., Manufacturing Pharmacists, Bristol, Tenn.-Va."

Inspectors were immediately dispatched to the firm's headquarters in Bristol and to branch offices in Kansas City, New York, and San Francisco. They found that the firm had already learned of the poisonous effects of the liquid sulfanilamide and had sent telegrams to more than 1,000 salesmen, druggists, and doctors. However, the telegrams merely requested the return of the product and failed to indicate the urgency of the situation or say that the drug was lethal. At FDA's insistence, the firm sent out a second wave of messages, worded more strongly: "Imperative you take up immediately all elixir sulfanilamide dispensed. Product may be dangerous to life. Return all stocks, our expense."

FDA then set out to make sure all of the drug was retrieved. Practically the entire field force of 239 FDA inspectors and chemists was assigned to the task. State and local health officials joined the search. Newspapers and radio stations continued to issue warnings.

The staff began by checking the company's shipping records and the distribution lists in the four distributing houses and in a number of wholesale and retail drugstores. Thousands of order slips were examined one by one. In one establishment alone, 20,000 sales slips were checked.

FDA employees tracked down the firm's 200 salesmen and questioned them about the dispersion of shipments and physician samples. Finding the salesmen was the first problem. In one typical case, a salesman was reported to be in a hotel in Washington, D.C. He was not there but forwarding addresses had been left for him in Jackson, Mich., and in Baltimore. These turned out to be for another man with the same name. Four days of searching finally found the man in University Park, MD. Once the salesmen were found, there was still the problem of getting the distribution information. One man in Texas, for instance, revealed the necessary information only after being jailed by state authorities.

In many cases, locating the purchasers of the elixir required some real detective work. In some drugstores, the elixir had been sold without prescriptions to purchasers whose names the druggist didn't know. In other cases, doctors had incomplete records--or none at all--of the names and addresses of patients for whom they had prescribed. In East St. Louis, Ill., for instance, 49 prescriptions were filled and the only identification on some were such notations as "Betty Jane, 9 months old," or "Mrs. Jackson (no address)."

Even when the purchaser was finally located, the inspectors frequently needed to do some ingenious questioning to determine what happened to the purchased elixir. One East St. Louis woman told an inspector she had destroyed the drug. The inspector persisted in his questions however. What did she mean "destroy"? Had she poured it down the sink? Had she buried it? No, the woman said, she had thrown the bottle out the window into an alley. The inspector found the bottle still unbroken, still containing enough elixir to kill any child intrigued enough to swallow its sweet, raspberry-flavored contents.

Many doctors and pharmacists did everything in their power to recover the elixir. One physician postponed his wedding to help an FDA chemist search for a 3-year-old boy whose family had moved into mountain country after obtaining a prescription.

Other physicians apparently were reluctant to admit that they had prescribed the drug, perhaps fearing they would be held accountable for its consequences. One inspector, checking out a Georgia drugstore, was told that a shipment of 1 gallon of elixir had been returned to the manufacturer after only 6 ounces had been dispensed. The patient who had taken the 6 ounces had suffered no ill effects, the druggist reported, and the inspector confirmed that this was true. But the inspector assigned to Bristol reported that 12 ounces was actually missing from the returned gallon, so the inspector in Georgia did some more questioning around town and tuned his ears to the local gossip. He learned that two other people had also bought the elixir. Both had died.

Similarly, a South Carolina doctor told an inspector that he had dispensed the medicine to only five people and none had died. But when the inspector began asking questions around town, someone told him of the death of a lumber mill employee. The inspector recognized the symptoms as those characteristic of Elixir Sulfanilamide poisoning. Through the mill superintendent, he located the employee's sister. Yes, she said, her brother had gone to the doctor and had been given some red medicine before he died. She told the inspector that, in accordance with custom, all medicines and sickroom utensils had been placed on the grave, about one and a half miles back in the fields. Accompanied by family and friends, the dead man's sister and the inspector walked to the wooded knoll. On the single mound of fresh earth were several bottles, dishes, spoons, and a 4-ounce bottle containing about 1 ounce of Elixir of Sulfanilamide. It bore the weathered but legible prescription label of the doctor. In fact, the inspector learned, four of the doctor's patients had died after taking the elixir.

Victims of Elixir Sulfanilamide poisoning--many of them children being treated for sore throats--were ill about 7 to 21 days. All exhibited similar symptoms, characteristic of kidney failure: stoppage of urine, severe abdominal pain, nausea, vomiting, stupor, and convulsions. They suffered intense and unrelenting pain. At the time there was no known antidote or treatment for

diethylene glycol poisoning.

In a letter to President Franklin D. Roosevelt, a woman described the death of her child:

"The first time I ever had occasion to call in a doctor for [Joan] and she was given Elixir of Sulfanilamide. All that is left to us is the caring for her little grave. Even the memory of her is mixed with sorrow for 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."

A few simple tests on experimental animals would have demonstrated the lethal properties of the elixir. Even a review of the current existing scientific literature would have shown that other studies--such as those reported in several medical journals--had indicated that diethylene glycol was toxic and could cause kidney damage or failure. But in 1937 the law did not prohibit the sale of dangerous, untested, or poisonous drugs. Dr. Samual Evans Massengill, the firm's owner, said: "My chemists and I deeply regret the fatal results, but there was no error in the manufacture of the product. We have been supplying a legitimate professional demand and not once could have foreseen the unlooked-for results. I do not feel that there was any responsibility on our part." The firm's chemist apparently did not share this feeling; Harold Watkins committed suicide after learning of the effects of his latest concoction.

Through the dogged persistence of federal, state, and local health agencies and the effects of the AMA and the news media, most of the elixir was recovered. Of 240 gallons manufactured and distributed, 234 gallons and 1 pint was retrieved; the remainder was consumed and caused the deaths of the victims.

Twenty-five seizures were made under federal law. The charge was misbranding. "Elixir," FDA said, implied the product was an alcoholic solution whereas it was, in fact, a diethylene glycol solution and contained no alcohol. If the product had been called a "solution" instead of an "elixir," no charge of violating the law could have been made. FDA would have had no legal authority to ensure the recovery of the drug and many more people probably would have died.

FDA Commissioner Walter Campbell, who was then pressing for better federal regulation of drugs, pointed out how the inadequacy of the law had contributed to the disaster. "It is unfortunate that under the terms of our present inadequate Federal law, the Food and Drug Administration is obliged to proceed against this product on a technical and trivial charge of misbranding. ...[The Elixir Sulfanilamide incident] emphasizes how essential it is to public welfare that the distribution of highly potent drugs should be controlled by an adequate Federal Food and Drug law. ... We should not lose sight of the fact that we had many deaths and cases of blindness resulting from the use of another new drug, dinitrophenol, which was recklessly placed upon the market some years ago. Deaths and blindness from this [drug] are continuing today. We also should remember the deaths resulting from damage to the liver that have occurred from cinchophen poisoning, a drug often recommended in such painful conditions as rheumatism. We also have unfortunate poisoning, acute and chronic, resulting from thyroid and radium preparations improperly administered to the public.

"These unfortunate occurrences may be expected to continue because new and relatively untried drug preparations are being manufactured almost daily at the whim of the individual manufacturer, and the damage to public health cannot accurately be estimated. The only remedy for such a situation is the enactment by Congress of an adequate and comprehensive national Food and Drugs Act which will require that all medicines placed upon the market shall be safe to use under the directions for use. ..."

As it turned out, the Elixir experience did more than hasten enactment of the 1938 Federal Food, Drug, and Cosmetic Act. The New Drug section, added to prevent such tragedies, gave the United States a new system of drug control which provided superior protection while stimulating medical research and progress. And 25 years later, it saved the Nation from an even greater drug tragedy--a thalidomide disaster--like that in Germany and England. Here again, history repeated itself. A pending bill, the Drug Amendments of 1962, was finally enacted.

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http://www.the-scientist.com/?articles.view/articleNo/35714/title/The-Elixir-Tragedy--1937/

The Elixir Tragedy, 1937

A mass poisoning of 105 patients treated with an untested medication spurred Congress to empower the US Food and Drug Administration to monitor drug safety.

By Jef Akst | June 1, 2013

The US Food and Drug Administration's role in the regulation of novel medicines was born out of tragedy. Seventy-one adults and 34 children died in the fall of 1937 after taking a drug called Elixir Sulfanilamide to treat a variety of ailments, from gonorrhea to sore throat. At that time, the FDA, which had been launched in 1906 as the Bureau of Chemistry, served simply to police claims made about food and drug ingredients. No formal government approval was required to market new drugs.

"The initial 1906 legislation was relatively weak," says Paul Wax, a medical toxicologist at the University of Texas Southwestern Medical Center. "There had to be some truth to what [drug companies] were selling . . . but in terms of safety, let alone efficacy, that wasn't part of the equation."

That all changed in 1938, after the deaths linked to Elixir Sulfanilamide had become a national scandal. Six years earlier, German pathologist and bacteriologist Gerhard Domagk discovered that a chemical called prontosil protected against certain bacterial infections in mice. Further research demonstrated that the compound's active ingredient, sulfanilimide, could fight streptococcal infections in humans, prompting several pharmaceutical companies—including Merck, Squibb, and Eli Lilly—to begin making sulfanilamide drugs. These medicines were

mostly formulated as capsules and tablets, but the S.E. Massengill Company of Bristol, Tennessee, decided that a liquid form of sulfanilamide could also be a big seller.

Massengill's chief chemist concocted a solution of 10 percent sulfanilamide, 72 percent diethylene glycol, and 16 percent water. The company's internal control lab approved the solution's appearance, taste, and fragrance—it was flavored with raspberry extract, saccharin, and caramel, among other ingredients—and by September 1937, Massengill had distributed 240 gallons of the liquid, called Elixir Sulfanilamide, across the country.

But commercial success soon soured, as the first deaths were reported in October: six patients in Tulsa, Oklahoma, died of renal failure following treatment with the drug. FDA Commissioner Walter Campbell immediately ordered the vast majority of the agency's 239 inspectors and chemists to investigate, and researchers quickly fingered the medicine's solvent, diethylene glycol, as the cause of the deaths. But under the regulations of the time, Massengill hadn't really done anything wrong: analyses of the concoction taken by the Tulsa patients revealed the ingredients to be exactly what the company had said they were. (The company had only broken the law by calling the medicine an "elixir," a designation that was reserved for drugs containing ethanol.)

The disaster provoked a public outcry that led to the passage of the 1938 Food, Drug, and Cosmetics Act, which gave the FDA power to monitor the safety of new drugs. "Unfortunately, it took a disaster like this to get the senators to vote and empower the FDA like it should have been empowered to begin with," says Wax, who has studied the Elixir Sulfanilamide tragedy (*Ann Intern Med*, 122:456-61, 1995). It wasn't until October 1962, however, that Congress passed the Kefauver-Harris Drug Amendments, requiring companies to provide evidence of efficacy, in addition to safety, for drug approval.