A clear, colorless, odorless substance with a slightly sweet taste, diethylene glycol seemed the perfect base for a marketable syrup.

Sweet Syrup of Death: The Elixir Sulfanilamide Tragedy

In June 1937, Harold Cole Watkins, chief chemist for the Tennessee-based drug manufacturer S.E. Massengill, was wrestling with a thorny challenge. A drug called sulfanilamide, one of the new class of sulfa "wonder" drugs, was proving to have almost miraculous effects on previously untreatable bacterial infections, from streptococcus to meningitis, and Massengill salesmen had come back from the field reporting that a liquid form of the drug would surely sell well. Company owner Samuel Massengill charged Watkins with the task of creating one.

The obstacle to this seemingly simple idea was that sulfanilamide, a derivative of water-resistant fabric dyes, is almost impossible to dissolve. Watkins, however, set his mind to the task and after a few weeks of testing found a solution: diethylene glycol.

A clear, colorless, odorless substance with a slightly sweet taste, diethylene glycol seemed the perfect base for a marketable syrup. On verifying that it would dissolve sulfanilamide, he prepared a formula of 72 percent diethylene glycol to 16 percent sulfanilamide, flavored it with raspberry syrup and sweetened it with saccharine, and labeled the concoction Elixir Sulfanilamide.

In doing this, Watkins was violating branding laws, for FDA rules said that any substance called "elixir" must be ethanol-based, and Elixir Sulfanilamide was not. This was not the main problem, though. The main problem was that diethylene glycol, a powerful solvent used in brake fluid and wallpaper stripper, is highly toxic. Watkins had performed no tests to see if the new substance was poisonous, nor had he heeded the existing scientific literature demonstrating that it was. He didn't have to. In 1937, no law existed in the United States that said a company had to show a substance was safe for use before selling it.

85 **1958**

The Pharmaceutical Manufacturers Association (now PhRMA) is founded in Washington, D.C.

86

With the enactment of the Food Additives Amendment, manufacturers of new food additives are required to establish safety. This leads directly to the creation in 1966 of the *Food Chemicals Codex*, a compilation of internationally recognized, independent standards for verifying the identity, purity and quality of food ingredients.

RIGHT: The diethylene glycol in Elixir Sulfanilamide killed more than 100 people, 34 of them children, in the 1930s. In response, the 1938 Food, Drug, & Cosmetic Act empowered FDA to enforce USP's tests and quality standards, including truthful and accurate labels.

87 **1959**

HIV-1 appears for the first time in Kinshasa in the Democratic Republic of the Congo. In all, WHO estimates that 76 million people have been infected with the virus, and about 33 million have died of HIV/AIDS, roughly 700,000 in the United States.

89

Nuclear magnetic resonance and magnetic resonance imaging revolutionize the practice of chemistry and medicine by providing fast, nondestructive, noninvasive means to observe matter from the atomic to the macroscopic scale.

88 1960

Mestranol/norethynodrel (Enovid), the first hormonal oral contraceptive, is introduced in the United States.

AFFIRMING THE MANDATE

The 1938 FD&C Act increased USP's relevance in public health crises by giving FDA greater power to enforce the compendium's quality standards. But to a large degree, the sections relating directly to USP simply continued the legal status granted in the 1906 Pure Food and Drug Act. That status, however, had been in serious peril in preceding years, so this affirmation that USP was to remain the official standard-setter for drug quality was not to be taken lightly.

The legislative challenges to public quality standards came from two directions.

First, earlier versions of the bill had allowed the Secretary of Agriculture to set its own standards and assays (tests for quality and impurities) in a wide range of situations. Given that many medical ingredients and almost all food ingredients fell under the Department of Agriculture's remit, this would have effectively allowed an end run around USP standards.

Second, calls for a governmental pharmacopeia had grown louder as politicians and industry leaders balked at this important federal role being given to a nongovernmental group. Despite USP's independent status that makes it free of political and corporate influence, and the organization operating at no expense to the American taxpayer, some influential groups endorsed a pharmacopeia created by "a properly organized governmental agency."

The Elixir Sulfanilamide tragedy put those notions to rest. The agonizing deaths of more than 100 people made clear the need for an independent group of top-level scientific experts who could give the federal government reliable quality standards for drugs and food ingredients. The 1938 Food, Drug, and Cosmetic Act not only retained mention of the USP, but cemented USP's status as the organization that set legal quality standards at the federal level. Over the next decades, the act was extended to give USP standards-setting power over dietary supplements, and a separate set of regulations gave legal authority to the food ingredients standards in the *Food Chemicals Codex* (*FCC*), acquired by USP in 2006. (The existence of an *FCC* monograph for a food ingredient does not provide independent evidence that a product may be lawfully marketed in the United States under the FD&C Act and its implementing regulations.)

In 1937, no law existed in the United States that said a company had to show a substance was safe for use before selling it.

People started to die the next month. FDA scientist Frances Oldham Kelsey (who some years later would save countless lives by refusing to grant approval to the antinauseant and sedative drug thalidomide) identified the diethylene glycol in Elixir Sulfanilamide as the culprit, and FDA launched a massive recall. But it could recall the drugs on only one basis: that S.E. Massengill had misbranded its bottles. By the time 236 gallons of the original 240 had been impounded on that technicality, more than 100 people had died, 34 of them children.

Samuel Massengill received a $26,000 fine. Harold Watkins committed suicide. And spurred by public outrage and grief, legislators in Washington finally passed a food and drug safety bill that had been hung up for years by political wrangling and industry resistance.

The 1938 FD&C Act both consolidated and expanded USP's official role in setting standards for drug and food ingredients, positioning the organization to be a much more meaningful actor in future public health crises. It maintained USP's roles of defining the "established name" and required characteristics of a drug, as well as specifying how drugs needed to be labeled, packaged and stored. By forbidding the Secretary of Agriculture to unilaterally amend assays or standards in the *USP*, it also gave USP greater autonomy and authority.

The new act required premarket approval of drugs by FDA and also made it illegal to manufacture an adulterated, misbranded or unsafe drug. (Manufacturers did not have to prove that a drug was actually *effective* until the passage of another piece of legislation, in 1962.) And, crucially, it gave FDA the power to enforce these rules. If a drug substance or product was tested and failed USP tests and quality standards, FDA could now take the all-important next step of recalling it from the market.

90 1961

Marshall Nirenberg and Heinrich Matthaei at NIH crack the human genetic code. Within five years, they have deciphered the 64 RNA three-letter codes for all 20 amino acids, making the language of DNA understandable.

91 1962

The newly enacted Kefauver-Harris Amendments impose a range of requirements aimed at ensuring the safety and efficacy of both new and existing drugs. As a consequence, USP's Committee of Scope sees its role reduced in selecting drugs deemed to represent "best practice and teaching of medicine."

92

A Drug Standards Laboratory is established through a partnership between USP, the American Medical Association (AMA) and APhA. The next year, the three agencies collaborate on USAN, the United States Adopted Names list of standard, universally agreed names for generic drugs. The USAN Council expands to include FDA in 1967.

The missing link in public health protection had been forged: USP's standards now had teeth.

This tragedy wasn't the last USP would see of deadly misuses of diethylene glycol. The substance's chemical similarity to the ubiquitous sweetener glycerin has made it the many-headed hydra of the drug world, and diethylene glycol–contaminated drugs have left a trail of destruction in their wake, especially in low- and middle-income countries with substandard quality-control procedures. South Africa, 1969: several children dead of contaminated over-the-counter sedatives. India, 1986: 21 dead from contaminated glycerin prescribed as a diuretic in hospitals. Nigeria, 1990: 47 dead from contaminated paracetamol syrup. Bangladesh, 1990 to 1992: 339 dead of the same syrup. Haiti, 1995: 85 children dead of adulterated acetaminophen syrup. Panama, 2006: 219 dead from glycerin in cough syrup adulterated with diethylene glycol.

In 2007, with the death toll mounting overseas, diethylene glycol made another appearance on American soil, when batches of contaminated low-cost toothpaste from Chinese manufacturers appeared at discount stores. Though there were no deaths or serious illnesses, FDA issued a recall and banned all toothpaste from China.

The incident prompted USP to provide one of the most urgently needed tools in addressing diethylene-glycol adulteration: better ways to distinguish it from glycerin and similar excipients (inactive ingredients used as sweeteners, coatings and the like). The revised glycerin standard became official May 1, 2009. New requirements forced drug-product makers to conduct an identity test for the presence of diethylene glycol in glycerin before they can use the glycerin in their products. USP also updated its monographs for several glycerin-based substances that are especially at risk for adulteration, including the popular sweeteners sorbitol and maltitol, commonly used in sugar-free foods and drugs.

When poor-quality products threatened patients' lives, USP standards helped contain public health crises and protect patients from future incidents.

1966

Csaba Horváth and Sandy Lipsky of Yale University publish a paper on the ion-exchange separation of organic compounds and one year later another on fast liquid chromatography. In 1969, they unveil high-performance liquid chromatography, an analytical technique included in USP monographs from 1975.

1965

Medicare (a health insurance program for those over 65, younger disabled people and dialysis patients) and Medicaid (health assistance for low-income people of all ages) are created. USP is tasked with developing categories and classes that may be used by prescription drug plans in developing their formularies for Medicare.

RIGHT: For over a century, USP and FDA have worked together to address urgent public health priorities. Here, U.S. President Barack Obama signs a 2011 executive order directing FDA to reduce drug shortages and prevent price gouging.

A RELATIONSHIP BOTH OLD AND NEW

As drugs, food and supplements, and devices change at an accelerated pace, USP's relationship with FDA is both expanding and shifting. The two organizations have been joined in federal law ever since the 1906 Pure Food and Drug Act gave FDA's precursor, the Bureau of Chemistry, the power to enforce the quality standards that USP had already been creating for more than 85 years. While USP, as the world's only nongovernmental, nonprofit pharmacopeia, is completely independent from FDA, the two have worked closely together on shared public health priorities, and they have developed a strong and constructive working relationship.

As independent, science-based organizations, USP and FDA do not always reach the same conclusion. One area of disagreement between them has been the application for biologic medicines, including biosimilars, of product-specific standards. It is USP's position that such standards are a foundational element in the country's proven system for ensuring the quality of biologic medicines and protecting patient safety, and that adherence to them should remain required. FDA disagrees and has twice supported proposed legislation that would exempt biologic medicines from having to comply with USP compendial standards.

For now, and while maintaining that adherence to public quality standards is an important patient safety protection, USP has announced that it will not publish as "official" any new product-specific standards for a biologic medicine unless there is support from stakeholders, including FDA and industry, to move forward with them.

In 2016, the U.S. Senate introduced the FDA and NIH Workforce Authorities Modernization Act, which proposed to exempt biologics and biosimilars from the longstanding law that requires drugs to meet USP quality standards. USP vigorously opposed this provision, with CEO Ron Piervincenzi saying at the time, "The proposal strips biologics of the protections provided by public quality standards and unravels a critical piece of the overall safety net for these drugs."

This provision was included again in section 207 of the Lower Health Care Costs Act, introduced in 2019 and being considered by the Senate at the time of writing this book. USP, along with many other organizations and agencies, has voiced strong concern about how this proposed exemption for biologics and biosimilars will affect patient safety and drug affordability. The implications for diabetics are especially immediate, since insulin was moved in March 2020 from being considered a drug, regulated by the 1938 Food, Drug, and Cosmetic Act, to a biologic, regulated by FDA's Center for Biologics Evaluation and Research. Although to date these legislative efforts have been unsuccessful, the point of disagreement continues.

Elizabeth Miller, formerly Vice President, U.S. Regulatory Affairs at USP and currently FDA's Assistant Commissioner for Medical Products and Tobacco Operations, helped USP expand and strengthen its relationships with various offices within FDA.

"Traditionally, we've been focused on the Center for Drug Evaluation and Research," says Miller. "But we're now building relationships with the Center for Food Safety and Applied Nutrition." Creating standards for the generic versions of therapies such as metered dose inhalers—which involve both a medical device and a drug—is more complex than for non-device–related drugs. It's no surprise, then, that USP is also building relationships with the Center for Devices as USP considers standards development for combination products and novel therapeutics, according to Miller. USP's challenge, she says, is to work with FDA on setting standards that give industry regulatory predictability, while allowing for new and better innovations in products to come to market.

"You want to give the industry enough information that they have the predictability," she says, "but also give the FDA enough latitude that there aren't specifications that would prevent them from approving something that is different but equally effective—and allowing it to be put into the market. We have to think about how we thread that needle."

95

1968

96

Marshall Nirenberg wins a Nobel Prize for his seminal work on the genetic code. He shares the award with Har Gobind Khorana (University of Wisconsin), who mastered the synthesis of nucleic acids, and Robert Holley (Cornell University), who discovered the chemical structure of transfer-RNA. Collectively, the three are recognized "for their interpretation of the genetic code and its function in protein synthesis."

Moving USP's headquarters from New York City to the American Society of Hospital Pharmacists building in Bethesda, Maryland, facilitates collaboration with FDA; Congress; local industry; and trade, scientific and consumer associations. In 1972, USP moves again, to nearby Rockville.

97

The Hong Kong flu outbreak kills one million people worldwide.

We began to realize the truly global nature of the excipient supply chain. The phenomenal number of handoffs increases the risks for adulteration and impact on public health.

CATHERINE SHEEHAN, PhD, SENIOR DIRECTOR, EXCIPIENTS

The presence of diethylene glycol in the toothpaste product, along with the additional diethylene-glycol adulteration cases seen around the world, shone a light on the unsettling new realities of protecting public health in an increasingly globalized pharmaceutical supply chain. Catherine Sheehan, a USP Senior Director responsible for excipients, points out that, for instance, the glycerin in the 2006 Panama diethylene-glycol tragedy was traced back to China.

"That's when we began to realize the truly global nature of the excipient supply chain," Sheehan says. "I think what alarmed everybody was the number of handoffs of the glycerin, from distributors to brokers and so forth, that circled the globe before it got to Panama. This phenomenal number of handoffs increases the risks for adulteration and impact on public health."

The challenges of protecting the quality of medicines in this era have put greater primacy on USP's role in the ecosystem of crisis response: developing new and better assays, updating its compendial monographs and general chapters, and making these new methods and standards available to pharmaceutical manufacturers and other stakeholders. While the *USP* has been continually revised since its inception in 1820, the new reality of supply chain interdependence has made these revisions more urgent and even lifesaving when it comes to responding to a public health crisis.

An Adulterated Milk Supply

Another public health crisis born of supply chain complexities took place in the same year as both the heparin adulteration episode and the reappearance of diethylene glycol in America. This time USP was spurred to augment its monograph revision response with even broader mechanisms to reinforce the safety of drug, food and dietary supplements ingredients.

98

1969

The *USP* is now recognized in 27 countries, serving as the sole standard in Costa Rica, El Salvador and Panama. USP accomplishes this with only ten full-time and three part-time employees.

99

1970

Executive director William Heller communicates a new direction for USP in serving global public health by setting standards for drugs not marketed in the U.S. Still an active volunteer, Dr. Heller has been serving USP for over 60 years.

100

Following a joint *USP-NF* panel to evaluate mechanisms for ensuring drug effectiveness, USP publishes an official dissolution test in 12 monographs. Over time, all oral drug productsinclude such a test, but if the drug does not exist in the *USP*, FDA's Office of Pharmaceutical Quality recommends dissolution test methods from its database.

In 2007, cats and dogs in the United States and Canada fell sick for unknown reasons. The culprit turned out to be wheat gluten deliberately adulterated with melamine, a chemical compound better known to the public as a component of Formica and dry-erase boards. The maker of the pet food in question pulled its products from the shelves, but not before hundreds of pets had died.

No sooner had the pet food mystery been solved, says Jeff Moore, USP's Senior Director of Scientific Strategy and Planning, than "the almost identical issue happened again. We hadn't even figured out how to solve the first one, and then we're seeing it again."

This time, the victims were people rather than pets. In September 2008, as many as 300,000 people in China, including 50,000 infants, became severely ill, developing agonizing urinary-tract stones and then kidney failure. Six babies died before the source of the problem was found: melamine. A company was deliberately adding cheaper melamine to milk and infant formula to bulk up the product in order to maximize its profits. The average person is familiar with melamine from countertops and other furniture veneers. Less well known is that it has 66 percent nitrogen, making it an effective and inexpensive mimic of protein content, which has traditionally been measured by assessing how much nitrogen is present.

"Our response to it was initially focused on, 'How do we fix this problem with better analytical methods?'" Moore says. This was a challenge in itself. As with both heparin and diethylene glycol, the testing procedures at the time were not designed to detect adulterants. Neither of the two tests commonly used by analysts could tell the difference between nitrogen from melamine and that from actual proteins.

In response, members of the USP Food Ingredients Intentional Adulterants Advisory Panel held a workshop in September 2009 to explore better

Supply chain interdependence has made revisions to the *USP* more urgent and even lifesaving when it comes to responding to a public health crisis.

methods of detecting falsified protein content in foods and ways to accelerate monograph changes relating to protein-testing methodologies. The workshop members settled on a toolbox of analytical solutions, including better protein-measurement assays, methods for detecting a variety of nitrogen-rich melamine-like compounds, and rapid non-targeted methods capable of uncovering unknown adulterants.

All of this became the work for a new group of experts, called the Skim Milk Powder Advisory Group, that USP convened in 2012. This group devised standardized tests that use ultra-high-performance liquid chromatography and tandem mass spectrometry to detect even minute amounts of nitrogen-containing adulterants added to milk to increase its apparent protein content. The group also developed a standardized non-targeted screening method for non-protein nitrogen compounds, which it published in the same year.

Having developed better testing methods, USP scientists then went several steps further, using research advances detailed in articles in *Journal of Agricultural and Food Chemistry* and *Journal of Food Composition and Analysis*.

First, to give laboratory professionals a way to make sure that they were not getting false negatives for melamine, USP supplemented the new testing methods with its first intentionally adulterated testing product. USP Skim Milk Powder with Melamine mimics the way skim milk powder would be illegally adulterated by adding melamine to liquid milk and then spray-drying the milk to produce a powder with a specific level of melamine. The product allows testers to see if their procedure is properly distinguishing melamine from protein. If their tests yield false negatives and they don't find the melamine in USP's adulterated powder, they know the tests are inadequate and could be allowing contaminated products into the marketplace.

LEFT: Children being tested for possible kidney stones at the Chengdu Children's Hospital in Sichuan, China, following melamine contamination of milk in 2008. Six babies died after drinking tainted milk powder, with more than 300,000 people affected.

1971–72

Biotechnology takes a major leap forward when Stanford's Paul Berg splices two DNA molecules, one from a tumor virus and one from a plasmid carrying E. coli genes, and a year later, his colleague Stanley Cohen and UC San Francisco's Herbert W. Boyer insert recombinant DNA into bacteria in such a way that the foreign DNA replicates naturally.

COMPOUNDING: CUSTOM MEDICATIONS

When public health disasters strike, attention naturally turns to the tragedy of mass deaths and the number of people affected. Harder to count are the lives saved and crises averted by the protective checks and balances within the American healthcare system, many of them underpinned by USP's quality standards.

The New England Compounding Center (NECC) tragedy of 2012, in which contaminated batches of a corticosteroid called methylprednisolone caused fungal meningitis in patients, provides a glimpse into the jeopardy to Americans' health that these checks and balances —including quality standards such as the *USP–NF's* General Chapter <797>—keep from becoming more than a tragic anomaly.

This important chapter, titled "Pharmaceutical Compounding—Sterile Preparations," lays out in 61 pages the minimum standards and practices that ensure environmental conditions and personnel competencies to minimize the risk of contaminating sterile preparations.

Public health officials inspecting the center after the outbreak found unsanitary conditions and identified no fewer than 18 types of fungi flourishing there. One of the officials went so far as to describe the laboratory as "a fungal zoo." It is little wonder, then, that at least two of these fungi made their way into the center's methylprednisolone acetate injection. Approximately 12,000 people were exposed, more than 700 became seriously ill or disabled and at least 64 died, making the NECC incident one of the worst drug disasters in U.S. history.

The criminal investigation that followed showed that the facility "improperly sterilized the methylprednisolone acetate, failed to verify the sterilization process, and improperly tested it to ensure sterility." USP experts were called to testify in the trial. According to Jeanne Sun, USP's Manager for Compounding, staff at NECC "were not following anything remotely close to [Chapter] <797>."

In November 2013, in response to the NECC disaster, Congress passed the Drug Quality and Security Act, legislation that granted FDA more authority to monitor and regulate the manufacturing of compounding drugs and that reaffirmed USP's role under its section 503A. USP sits on the Pharmacy Compounding Advisory Committee along with other stakeholders that provide advice on scientific, technical and medical issues concerning drug compounding and make appropriate recommendations to the Commissioner of Food and Drugs. At the state level, many governments have specifically incorporated references to USP general chapters in their laws and regulations; for example, according to the 2016 NABP Survey of Pharmacy Law, more than half of the U.S. State Boards of Pharmacy require compliance with General Chapter <797>.

1972

USP begins the Drug Product Defect (later Problem) Reporting Program, under contract to FDA. In 1975, FDA awards USP a special citation for its contribution to the program. The partnership ends in the mid-1980s with both agencies providing their own separate reporting programs.

LEFT: During the fungal meningitis outbreak of 2012, FDA and the Centers for Disease Control confirmed the presence of Exserohilum rostratum in unopened medication vials of preservative-free methylprednisolone acetate.