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When I use a word . . . Medicines regulation—diethylene glycol

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In 1937, when diethylene glycol was used as a solvent in the preparation of a medicinal product, an elixir of sulfanilamide, resulting in deaths, public outcry hastened the promulgation of an act that had been in preparation in the USA for several years, but which had met with opposition from pharmaceutical companies. The 1938 Food, Drug, and Cosmetics Act, as it was known, gave greater powers to the then recently formed Food and Drug Administration (FDA) in regulating the contents of medicinal formulations. Nevertheless, although similar regulatory systems have since been established around the world, episodes of poisoning with diethylene glycol in pharmaceutical formulations, whether deliberately included adulteration or as a contaminant, continue to be reported, generally in developing countries, usually affecting children, and often causing deaths.

Medicines regulation

Medicines regulation has been with us almost since medicines first started to be used.[1] Early regulation was mostly concerned with who supplied what,[2] and sometimes involved power struggles between physicians and apothecaries[3] or, later, pharmacists.[4] Sometimes concern focused on the costs of medicines, as for example at the start of the 20th century, when the British Medical Association published two volumes of information about patent medicines, their contents, and their true costs—*Secret Remedies* (1909) and *More Secret Remedies* (1912)—comparing the prices that manufacturers charged with the true costs of the ingredients.[5]

However, it would be some time before the overall quality, efficacy, and safety of medicinal products became the main concerns of medicines regulators, although from time to time concerns about the adverse effects of specific medicines led to individual pieces of legislation. For example, the 1851 Sale of Arsenic Regulation Act was enacted in the UK in order to reduce the risks of criminal arsenic poisoning, the 1861 Offences Against the Person Act criminalised the malicious administration of poisons, and the various Dangerous Drugs Acts of the 1920s limited the supply of drugs such as morphine, heroin, cocaine, and amphetamines.[6] Diethylene glycol affords an important example of medicines regulation in the USA in response to adverse reactions in the early 20th century: the 1938 US Food, Drug, and Cosmetic Act.

Diethylene glycol

Diethylene glycol is a relatively simple molecule, $C_4H_{10}O_3$. A liquid, it is itself soluble in water and organic liquids such as alcohol, ether, and acetone, and has been widely used as an organic solvent. It has also been used as a sweetener in wines and has been found as a contaminant in beers after use as a coolant in the brewing process.

For many years concerns had been growing in the USA about the poor quality of foodstuffs and adverse effects of marketed medicines, culminating in the 1906 Pure Food and Drugs Act and the establishment of the Bureau of Chemistry, the forerunner of the Federal Food and Drug Administration (FDA), which was established as the Food, Drug, and Insecticide Administration (FDIA) in 1927 and renamed the FDA in 1930.[7]

However, the 1906 act had several inadequacies. Although it prohibited false and misleading statements about the ingredients of a medicinal product, it did not prohibit fraudulent claims about a medicine's therapeutic uses. Furthermore, the Bureau had no power to enforce changes, but instead had to proceed against a company through the courts, where it was hard to prove intent on the part of the manufacturer to defraud the consumer, and the financial penalties, in the case of a successful prosecution, were nugatory.

In 1933, therefore, a new food and drug bill was drafted, with the intention of strengthening the powers of the FDA. However, the FDA, a federal agency, was prohibited by law from lobbying in favour of the bill, which was, of course, opposed by pharmaceutical manufacturers. Alterations to the bill to appease the manufacturers led to loss of support elsewhere, and the bill failed to progress.

However, a turning point came in 1937, when a pharmaceutical manufacturer, the Tennessee company S E Massengill, manufactured and marketed a medicinal product, Elixir Sulfanilamide, that consisted of sulfanilamide dissolved in diethylene glycol.[8] It was intended that this liquid formulation would encourage adherence to therapy, particularly in children. It had therefore been tested for flavour, appearance, and fragrance, but not for adverse effects, testing for which was not at that time required by law. After taking the drug, over 100 patients died; many were children who had been given Elixir Sulfanilamide for sore throats and coughs.

The FDA asked the manufacturers to withdraw the formulation, and public outrage created support for the proposed legislation to reinforce control of medicines.[9] And so, the US 1938 Food, Drug, and Cosmetic Act came into being and is still the legal foundation in the USA for the public control of drugs and devices intended to be used in the diagnosis, cure, amelioration, treatment, or prevention of disease in humans or animals. The act has been a model for similar legislation in many other countries.

The act prohibited traffic in new drugs, unless they were safe under the conditions of use described on their labels. It also explicitly required the labelling of drug products with adequate directions for use. The burden of proof that new drugs caused harm was

laid on the FDA, and companies that wanted to manufacture and market new drugs had to investigate their safety and report their findings to the agency. Unless the agency, within a specified period of time, found that the safety of a drug had not been established, the company could market it. The FDA was also authorised to remove from the market any drug it could prove to be unsafe.[10]

In 1941, the US Supreme Court also established, in a legal case concerning drug adulteration, that responsible individuals in a company could be held personally accountable for the quality of the products the company manufactured, and that distributors of pharmaceuticals were responsible for the quality of their products, even if they were manufactured elsewhere.[11]

Adverse effects of diethylene glycol

The adverse effects of diethylene glycol have been described to occur in three phases of increasing intensity[12]:

(a) gastrointestinal symptoms, such as nausea, vomiting, abdominal pain, and diarrhoea, and metabolic acidosis;

(b) severe metabolic acidosis and renal damage, which can be fatal; hypertension, cardiac arrhythmias, pancreatitis, and hyperkalemia or hyponatremia can also occur;

(c) delayed neurological effects, sometimes fatal.

Since the 1937 outbreak, several outbreaks of diethylene glycol poisoning have been reported in the following countries, mostly in children, and including deaths:

1969: South Africa (in over-the-counter sedatives)

1985: Spain (in topical silver sulfadiazine)

1986: India (in glycerin as an osmotic diuretic)

1990: Nigeria (in paracetamol)

1995: Bangladesh (in paracetamol)

1992: Argentina (in propolis)

1992: Venezuela (in paracetamol and vitamin syrups)

1995: Haiti (in paracetamol)

1998: India (in cough syrup and paracetamol syrup)

2004: France (in a herbal remedy)

2006: Panama (in cough syrup)

2008: Nigeria (in cough syrup)

2020: India (in cough syrup)

2022: Uzbekistan, Gambia, and Indonesia (in cough and cold syrups)

Causes and prevention

The authors of a systematic review of the published literature found that most cases have occurred in developing countries.[13] They suggested that the presence of diethylene glycol in medicinal products arises in two main ways:

- through deception about the true nature of certain ingredients by individuals during the pharmaceutical manufacturing process, i.e. adulteration;
- through failure to adhere to standardised quality control procedures in manufacturing pharmaceutical products, i.e. contamination.

For prevention they suggested enforcement of quality control procedures by any individual or company involved in producing pharmaceutical products, coupled with national regulatory oversight of pharmaceutical manufacturers.

Further reading

More details about the 1938 act and later developments can be found in references.[14],[15],[16]

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