Medicines legislation and regulation in England, 1500–2020

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Abstract
The initial purposes of regulation of medicines in England were principally to raise government revenue, to discourage murder by poisoning, and to regulate the activities of pharmacists. It was only much later that regulators sought to ensure that medicines were of good quality, reasonably safe, and at least somewhat effective, and to regulate misuse of drugs. Here we survey the history of the regulation of medicines and poisons in England from the perspective of clinicians with an interest in therapeutics (See Table 1).

<<Table 1 near here>>

Part 1: Legislation before 1900

16th century

Pharmacy Wares, Drugs, and Stuffs Act 1540

King Henry VIII had founded the College (now the Royal College) of Physicians in 1518 and promulgated this Act to empower the physicians to inspect apothecaries' wares and destroy them if defective. Until then the apothecaries, who had originally purveyed non-perishable commodities—spices, drugs, comfits, preserves, and the like—and had gradually focussed on medicines, had been independent practitioners who prepared and sold drugs for medicinal purposes. Although the apothecaries were keen to be recognized as independent practitioners, their requests were refused until 1617, when James I founded the Worshipful Society of the Art and Mistery of Apothecaries. The struggle between the physicians and the apothecaries eventually led the former to publish the *Pharmacopoeia Londinensis* in 1618.[1]

18th Century

The Stamp Act 1783

One way in which 18th century governments sought to raise income was to require certain transactions and some goods for sale to carry a tax receipt in the form of a stamp. They also required vendors to buy an annual licence. The stamp duty, first extended to proprietary medicines ("quack medicines" as Lord John Cavendish called them) in 1783,[23] was administered by the Board of Stamps through the Stamp Office. This existed alongside the Post Office, Tax Office, Salt Office, and Hawkers' and Pedlars' Office as part of the machinery of taxation. By 1795–96, stamp duty raised over £1.7m net,[4] about £205 million at current value.[5]

The primary aim was to pay for government expenditure. A contemporary pamphlet declared that the Act 'put His Majesty into the disagreeable situation of signing a decree, that no sick or lame person, or diseased cattle, in Great Britain, shall have a medicine of repute without paying tribute.'[6] However, the 1783 Act exempted medicines prepared by those 'bred to the profession of physician or apothecary.'[7 8] That is, the Act favoured those with some expertise, at the expense of the purveyors of nostrums.

19th Century

Further Stamp Acts

The 18th century acts were repealed by later acts, promulgated in 1802, 1804, and 1812.[9] The Schedule to the 1802 Medicines Stamp Act ran from Asiatic Bilious Pills and Anti-

Hysteric Pills, via the Elixir of Longevity or Swedish Preservative and the Vinegar of Four Thieves, to Zimmerman's Stimulating Fluid[10]; only mineral waters were exempt. The Act also provided for stamp duty to be levied on 'any preparation [that] is "held out or recommended to the public", by advertisement or otherwise, "as Nostrums or Proprietary Medicines, or as Specifics, or as beneficial to the Prevention, Cure, or Relief of any Distemper, Malady, Ailment, Disorder, or Complaint."[11] [A]

It took until the Stamp Act of 1815 to disentangle ginger or peppermint lozenges sold as 'Articles of Confectionery' from the same lozenges sold 'for the Prevention, Cure, or Relief of any Distemper, Malady, Ailment or Disorder incident to or in any wise affecting the Human Body.' [12] [13]

The term 'ailment' in the Act continued to be applied by the Commissioners of Customs and Excise to conditions such as freckles, insect bites, or discolouration of the teeth until 1929, when remedies for these conditions became exempt from duty.

An unintended consequence of the Stamp Acts was that proprietary medicines whose contents were not disclosed, but which were proffered for sale with claims of therapeutic efficacy, now bore a government stamp that signified, if not endorsement of the claims, at least acquiescence in them. These 'secret remedies' were commonly called 'patent medicines', although an editorial in 1846 pointed out that 'It is a popular error to suppose that the quack nostrums, so abundant in the present day, are in any way protected by Royal Letters Patent, or, indeed, enjoy any protection at all. It is a fact that not one of the so-called "Patent" medicines in present vogue is protected by patent.'[14] Their sales were sustained by advertising, revenue from which in turn sustained provincial newspapers.[15]

The claims made by manufacturers of patent medicines were for the most part both unbelievable and, by the 19th century, exceptionally profitable. Beecham's Pills ('Pink Pills for Pale People') were advertised to cure 'Constipation, Headache, Dizziness or Swimming in the Head, Wind, Pain, and Spasms at the Stomach, Pains in the Back, Restlessness, Insomnia, Indigestion, Want of Appetite, Fullness after Meals, Vomitings, Sickness of the Stomach, Bilious or Liver Complaints. Sick Headaches, Cold Chills, Flushings of Heat, Lowness of Spirits, and all Nervous Affections, Scurvy and Scorbutic Affections, Pimples and Blotches on the Skin, Bad Legs, Ulcers, Wounds, Maladies of Indiscretion, Kidney and Urinary Disorders, and Menstrual Derangements.'[16] The pills contained aloes, powdered ginger, and soap. Thomas Holloway's Pills, whose contents were similar, and Holloway's Universal Family Ointment, provided him with the fortune that allowed him to found Royal Holloway College in the University of London and a sanatorium at Virginia Water.[17]

[A] In the case of The King *v* Southerton, the defendant, an attorney, threatened 'to put in motion a prosecution by a public officer to recover penalties for selling Fryar's Balsam without a stamp, (which by stat. 42 Geo. 3, c. 56, is prohibited to be vended without a stamped label,) for the purpose of obtaining money to stay the prosecution.' Although not convicted, Southerton was struck off the Roll of Attorneys. [The King v. Southerton, Court of King's Bench. English Reports 1805; 102:1235-42. https://vlex.co.uk/vid/the-king-against-southerton-803365993]

The much-needed revenue from stamp duty had to be set against manifest profiteering by the manufacturers of proprietary medicines, harm to the public health, and detriment to pharmacists. This led to stormy debate in Parliament when the abolition of stamp duty on proprietary medicines was discussed in 1939. It led Sir Arnold Wilson to remark: 'I do not think there can ever have been an occasion in this House within living memory when more than 200 Members have begged the Chancellor of the Exchequer to continue a tax and not to repeal it.' Stamp duty on medicines was finally abolished in 1941.

Sale of Arsenic Regulation Act 1851

The 19th century saw some progress in legislation to safeguard the public regarding medicines with beneficial pharmacological actions that were also potential poisons—opiates, digitalis, and salts of mercury and antimony, for example. Public disquiet was the stimulus: 'The number of murders which had been perpetrated recently by poison, which could be procured with facility, particularly in the districts where it was used for agricultural purposes, was so great that he was sure the House would agree with him in the necessity of putting a stop to it.'[18] The first control was the Sale of Arsenic Regulation Act, 1851.[19] It did not cover other poisons, but '… arsenic, from the comparative absence of taste and colour, afforded great facilities for the commission of the crime of poisoning ... a substance which … might be used for the purposes of crime with fatal facility.'[20] The Act permitted the sale of arsenic only to persons known to the vendor, or to a person vouching for the purchaser; and then only if details were recorded in a Poisons Book.

Medical Acts 1858 and 1862

The *British Pharmacopoeia* (*Pharmacopoeia Britannica*) was recommended and announced in the Medical Acts of 1858 and 1862 respectively: it appeared in 1864 and is still in use today.

Offences Against the Person Act 1861

The wide-ranging Offences Against the Person Act of 1861[21] set out in statute crimes such as causing 'grievous bodily harm'. The Act also made 'Maliciously administering Poison, &c. so as to endanger Life or inflict grievous bodily Harm' a statutory offence, and specifically made the use or attempted use of 'Chloroform, Laudanum, or other stupefying or overpowering Drug' with the intention of committing an offence an offence.

Poisons and Pharmacy Act 1868

The Poisons and Pharmacy Act 1868 recognized that 'it is expedient for the safety of the public that persons keeping open shop for the retailing, dispensing, or compounding of poisons, and persons known as chemists and druggists, should possess a competent practical knowledge of their business, and to that end … should, before commencing such business, be duly examined as to their practical knowledge, and that a register should be kept …'.[22] Examination and registration were to be undertaken by the Pharmaceutical Society, who would receive a fee for these activities. The Act contained a schedule of poisons, including arsenic, cyanides, aconite, and strychnine, but also cantharides and ergot

of rye.[B] The Privy Council was empowered to add poisons to the schedule, but was reluctant to do so. Carbolic acid (phenol), which was responsible for a 'large number of painful deaths', had still not been scheduled in 1899, except in Ireland, despite the urging of many coroners and the Pharmaceutical Society.[23] The 1868 Act also extended to medicines the provisions of the Adulteration of Food and Drink Act 1860, defining adulteration as 'an admixture injurious to health.'

The full force of the 1868 Act to limit the sale of medicines containing poisons took 25 years to be felt. Continued lobbying against proprietary ("patent") medicines by, among others, the British Medical Association, and deaths from poisonous remedies, led to questions in the House of Commons.[24] [25] The Pharmaceutical Society in 1892 prosecuted five firms of grocers under the Pharmacy Act 1868 for selling a poison,[26] namely chlorodyne, which contained opium and chloroform.[27] While medicines that were patented were exempt, so-called 'patent medicines', such as Dr Collis Browne's Chlorodyne, whose ingredients were secret, held no patent, and therefore came within the provisions of the 1868 Act, and those containing a poison could only be lawfully sold by a pharmacist.[28, C] In consequence morphine was removed from many patent medicines and sales declined.

Sale of Food and Drugs Acts 1875 and 1879

These acts dealt with adulteration of food and drugs.[29] The extent of the practice had been uncovered by the Lancet's Analytical Sanitary Commission, directed by Dr Hassall, which found that many foodstuffs were often adulterated.[30] The foodstuffs mentioned included coffee, sugar, arrow-root, pepper, mustard, chicory, bread, oatmeal, tea, cocoa, milk, isinglass, vinegar, pickles, ginger, cinnamon, nutmegs, mace, cloves, pimento, mixed spice, and many others.

A Bill to Restrict the Sale of Patent Medicines 1884

The Preamble to this Bill, which never passed into law, began: 'Whereas patent medicines containing poison have caused sickness and death …'.[31] It proposed that the Pharmaceutical Society of Great Britain should analyse any patent medicine at the request of any vendor or purchaser. The bill failed, because of opposition from the Society of Chemists and Druggists.

Indecent Advertisements Act 1889

The then Member of Parliament for Flintshire, Samuel Smith, had told the House in 1888 that 'The streets were polluted with the advertisements of quack doctors. One of the greatest evils of late years had been the great increase of quack advertisements of a filthy kind. It was remarked to him the other day, by a gentleman who had spent much time on the Continent, that whereas in Germany he never knew one of these indecent

[B] A Thomas Teague, who ran a beer shop, was fined £5 for allowing his daughter to sell packets of 'a compound of arsenic and sulphur, each packet containing sufficient arsenic to poison over a hundred persons,' to a stranger. [Anonymous. Illegal sale of poisons. Law Journal 1876; (8 January):15.]

[C] A sequel to this decision was the conviction in 1929 under the Merchandise Marks Act of Hankinsons, Ltd, Chemists, for selling a mixture labelled 'Chlorodyne BP, 85' that contained no morphine. (Sale of Chlorodyne. Prosecution for false traded description. The Times 26 July, 1929: 11.)

advertisements to be thrust in his hand, when he came to London such advertisements were thrust into his hand frequently.'[32] The advertisements 'made statements with regard to secret diseases which were frequently untrue, and which were mostly intended to induce to impurity of life, and also by working upon the fears of the readers to terrify them into consulting the medical quacks whose names might be on the pamphlets.' A Bill was introduced to limit the distribution of indecent advertisements, although The Earl of Wemyss worried that a 'prudish policeman might … bring a person before a magistrate for displaying a representation of the Venus de Medici.'[33] The Indecent Advertisements Act did not apply to newspaper advertisements, and so was largely ineffectual in curbing the advertising of largely ineffective cures for venereal diseases.[D]

Medicines legislation at the end of the 19th century

To summarize, medicines legislation in the 18th and 19th centuries failed to protect the public from harmful medicines, and did nothing to test whether medicines had the therapeutic properties claimed, but made progress in curtailing the widespread sale of poisons and explicitly making the adulteration of medicines unlawful.

The public gained some protection through restrictions on those responsible for dispensing medicines by the Pharmacy Act 1852[34] and its successors;[35] and through restrictions on prescribing by the Medical Act 1858. The latter required doctors to be registered as medical practitioners with the General Medical Council and provided that 'no Person shall be entitled to recover any Charge in any Court of Law for ... any Medicine which he shall have both prescribed and supplied, unless he shall prove upon the Trial that he is registered under this Act.'[36]

The struggle to control patent medicines persisted throughout the 19th century and well into the 20th, leading to the failure of the 1931 Patent Medicines Bill and the relative success of the 1941 Pharmacy and Medicines Act (both discussed below).

[D] In a Scottish case from 1892, James Dingwall handed a man called Thomas Murray a pamphlet titled *The Guide to Reason*, 'relating to nervous debility, or other complaint or infirmity arising from, or relating to, sexual intercourse' and was found guilty at the Sherriff's court of contravening the 1889 Act. His conviction was quashed by the Court of Justiciary, which found that the indictment had not stated that the book was obscene, indecent, or an advertisement [Dingwall v Stevenson. Sessions Cases Court of Justiciary (Rettie) 1892:16.]

Part 2: Legislation after 1900

The 20th century

Poisons and Pharmacy Act 1908

This Act was intended 'to Regulate the Sale of certain Poisonous Substances and to Amend the Pharmacy Acts.'[37] It contained a schedule of poisons, divided into Part I and Part II, and imposed additional restrictions on the sale of poisons in Part 1. 'As to Poisons in both parts of the Schedule the vessel, wrapper, or cover containing them has to bear a label distinctly stating — (a) The name of the article; (b) The word "Poison."' The poisons listed in Part I of the Schedule included arsenic and its medicinal preparations (but not, for example, agricultural preparations of arsenic), 'all poisonous vegetable alkaloids not specifically named', cocaine, opium, prussic acid (hydrocyanic acid), and some other poisons. For many poisons, it stipulated a minimum concentration that must be exceeded for it to fall within the scope of the Act. A vendor required a licence to sell poisons.

Defence of the Realm Act 1914

This wartime legislation was enacted a few days after Britain's entry into the First World War. It enabled the Government to make emergency provisions, as the need arose, to serve the war effort. The Army Council Orders of 11 May 1916[38] issued under the Act, and subsequent additions and amendments,[39] [40] made the sale of certain drugs—including cocain [*sic*], Indian hemp, and morphine—to any member of his Majesty's Forces, except doctors, dentists, and veterinary surgeons—an offence, unless prescribed by a registered medical practitioner.[41] Further proclamations prohibited 'The importation of cocaine and opium into the United Kingdom.' [42]

Venereal Disease Act 1917

Captain Frederick Guest told the House of Commons in 1917 that 'during the course of the War it is no exaggeration to say that between 40 000 and 50 000 cases of syphilis have passed through our hospitals in France', and there were nearly four times as many cases of gonorrhoea.[43] Concerns that sexually transmitted diseases were compromising the army's fighting fitness led to more effective legislation against quack cures for venereal diseases. The government introduced a very wide Criminal Law Amendment Bill, which dealt with various sexual offences and also prohibited indecent advertisements.[44] The provisions relating to treatment later formed the basis for the Venereal Disease Act 1917 'to prevent the treatment of Venereal Disease otherwise than by duly qualified medical Practitioners, and to control the supply of Remedies therefor; and for other matters connected therewith.'[45] The 1917 Act prohibited the advertising to the public of 'any pills, capsules, powders, lozenges, tinctures, potions, cordials, electuaries, plaisters [*sic*], unguents, salves, ointments, drops, lotions, oils, spirits, medicated herbs and waters, chemical and officinal preparations whatsoever' for any venereal disease. It also made it an offence for anyone other than a duly qualified medical practitioner to treat anyone for venereal disease for reward.

Dangerous Drugs Act 1920 and subsequent Acts

The problem of dangerous drugs had not begun with the First World War, and did not disappear with the Armistice in November 1918. The Royal Commission on Opium in 1895 had found the arguments for prohibiting the opium trade unconvincing.[46] Besides, '… the revenue derived from opium [was] indispensable for carrying on with efficiency the Government of India.'[47] The Shanghai International Opium Commission of 1909 and the International Opium Convention of 1912 sought cooperation on the suppression of opium, morphine, and cocaine.[48] [49] Ratification of the 1912 Convention had been one of the Articles of the Peace Treaties signed after the War, so that the British, as signatories, [50] were obliged to take action, as the memorandum to the Dangerous Drugs Bill recognized.[51] There followed three Dangerous Drugs Acts in five years, intended to reduce the trade in drugs. The 1920 Act prohibited the import and export of opium, cocaine, and some derivatives, replacing the prohibition brought in under the Defence of the Realm Act 1914 (DORA).[52] This first incarnation of the Dangerous Drugs Act proved unpopular with the British Medical Association, who had not been consulted and who pointed to practical difficulties in its implementation and to the burden it placed on the dispensing doctor.[53] A second Act followed in 1923. In 1924, Sir Humphry Rolleston chaired a Committee appointed by the Minister of Health 'to consider and advise as to the circumstances, if any, in which the supply of morphine and heroin … to persons suffering from addiction to those drugs may be regarded as medically advisable …'.[54] That matter is still debated. Further legislation followed in 1925, principally to bring into effect the provisions of the 1925 Geneva Convention.[55] The Act came into force in 1928, and further regulations extended restrictions to include coca leaves and cannabis (Indian hemp).[56] [57] There followed a series of acts that sought to reduce the harm from dangerous drugs.

The Drugs (Prevention of Misuse) Act 1964 was a short-lived measure to restrict the use of amphetamines. At least part of the rationale was that "pep pills" were connected with hooliganism. 'One had only to read of the unfortunate affair which occurred at Clacton—where, as far as I know, there was very little alcoholism, and where the young people taking part were "lit up" with these pep pills—to realise the connection.'[58] It was repealed when the Act was brought up to date in 1965 and 1967. The efficacy of the measures was unclear. The number of those convicted under the Dangerous Drugs Act 1965 rose from 4702 in 1969 to 6921 in 1970.

Therapeutic Substances Act 1925 and Therapeutic Substances (Prevention of Misuse) Acts, 1947 to 1953

The Therapeutic Substances Act was brought in to control the quality and authenticity of those therapeutic materials for which it was impossible to carry out the direct chemical and physical tests specified in the *British Pharmacopoeia*.[59] The need to standardize medicines such as digoxin and anti-tetanus serum had been discussed in 1909, but the War had halted progress. In 1920 a departmental committee proposed definition of standards, provision of systems to ensure that the standards were met, and steps to prevent foreign medicines from circumventing the standards. Nevertheless, the legislation was delayed until proposals by the League of Nations made it essential, if British medicines were still to be exported to Europe. A Joint Committee, aided by an Advisory Committee, was empowered by the Act to

set standards (including 'sell-by' dates), to regulate testing, and to grant licences. The work was initially entrusted to the Pharmaceutical Society.

Proprietary Medicines Bill 1931

Neither the Pharmacy Acts nor the Medical Act stemmed the tide of proprietary medicines advertised directly to the public. The clamour over 'patent medicines', louder in the USA, initially fuelled by Samuel Hopkins Adams's series of 11 articles in *Colliers Weekly* in *1905–6*, later gathered into a volume titled *The Great American Fraud* (1912), was heard in England too.[60] [61] At the beginning of the 20th century, the British Medical Association published analyses of many 'secret remedies,' and showed them to be mostly therapeutically worthless and exorbitant when the net ingredient cost was compared with the sale price.[16] [62] In the aftermath, a select committee was established in 1912 to make recommendations. The Committee held 33 sessions, examined 42 witnesses, and asked more than 14 000 questions.[63] The Committee 'found much difficulty in arriving at a clear appreciation of the law [regulating medicines in the United Kingdom] and its administration.' The first of its 13 recommendations was that 'the law governing the advertisement and sale of patent, secret and proprietary medicines and appliances be coordinated and combined under the authority of one Department of State.' It also recommended that the ingredients and their proportions in every remedy and a full statement of the therapeutic claims made, be submitted (confidentially) to the Department. However, the report was published on 4 August 1914, at the outbreak of the First World War, and little came of it. An attempt in 1920 by Lord Astor to introduce a Proprietary Medicines Act failed.[64]

The recommendations of the Select Committee on Proprietary Medicines had been largely eclipsed by the events of the First World War, and the problem of proprietary medicines persisted. The Proprietary Medicines Bill 1931 represented a further failed attempt 'to regulate the manufacture, sale, and advertisement of certain medicines and surgical appliances; and for purposes connected therewith.'[65]

Pharmacy and Poisons Act 1933

The Pharmacy Act 1852, and the related Acts of 1868 and 1908, left enforcement of the law and control of the sale of poisons in the hands of the Pharmaceutical Society.[E] However, the Government 'felt that a non-official association with insufficient resources was not the right body to regulate matters affecting large sections of the public and matters immediately bound up with the health and safety of the public.'[66] This Act therefore transferred the duty of determining what were poisons and of administering the law to the Home Secretary, assisted by a Poisons Board, which comprised 'representatives of medicine and pharmacy, technical experts and representatives of the Government Departments concerned.' The Poisons List specified those substances that fell within the scope of the Act. The Poisons List was updated in 1971[67] and the Act was replaced by the Poisons Act 1972.

[E] In 1953, the Pharmaceutical Society exercised their duty 'to take all reasonable steps to enforce the provisions of the Act' when they took to court Boots the Chemist, who had introduced a 'self-service' pharmacy. The Pharmaceutical Society argued that it was unlawful to sell any poison unless 'the sale is effected by, or under the supervision of, a registered pharmacist.' The Court of Appeal disagreed. [Pharmaceutical Society of Great Britain v Boots Cash Chemists (Southern) Ltd. England & Wales Court of Appeal Civil. 1953;6 (05 February).]

Medicines and Surgical Appliances (Advertisement) Bill 1936

This bill sought 'merely to remove some of the worst abuses that exist in connection with the advertisement and sale of patent medicines and secret remedies.'[68] 'Opposition to the Bill was, however, whipped up against conventional medicine by psychic healers, anti-vivisectionists, and other groups, so that at the second reading in March 1936 the Bill was opposed and the House was counted out during the ensuing debate. The immediate reason for this fate was that the Bill came up for its second reading on the day of the Grand National!'[69]

The problem of the 'quack medicine trade' persisted. A Select Committee on Medicine Stamp Duties reported in 1936.[70] It concluded that 'Should control of the trade in medicines and appliances be deemed desirable, for the protection of the public, Your Committee believe that the best method of achieving this would be a system of examination and registration of all advertised medicines and appliances.' In a debate in the House of Lords in 1938, the distinguished physician Lord Horder called attention to the deleterious effects of quack medicines on public health.[71] He referred to the vested interests 'of newspapers and their proprietors, the large Press agencies, and those who own hoardings and posters, for it is becoming more and more obvious that the head and front of the offence in the matter of quack medicines is not the medicine but the advertisement, so often grossly misleading if not actually fraudulent.' In spite of Lord Horder's desire to see quack medicines regulated, Viscount Gage argued that 'the orthodox school of medicine—although I think everybody accorded it a great measure of respect whether he agreed with the orthodox school or not—should not be allowed to establish too rigid a dictatorship over other schools of thought'; no legislation followed.

Food and Drugs Act 1938

Much of the 1938 Food and Drugs Act was concerned with 'slaughterhouses and knacker's yards.' Section 3 of the Act prohibited the sale of any drug not of the nature, substance, or quality demanded, which admirable provision was largely negated by Section 4, which provided a defence when 'the article supplied was a proprietary medicine and was supplied in response to a demand for that medicine.'[72]

Cancer Act 1939

The principal aim of the Cancer Act 1939 was to provide for 'the earlier and more effective treatment of cancer.'[73] It made local authorities responsible for the provision of adequate facilities for the diagnosis and treatment of cancer, and it allowed the Minister of Health to make loans to the National Radium Trust to buy radiopharmaceuticals.[74] Section 4 of the Act, however, made it an offence to take part in the publication of any advertisement containing an offer to any person to treat, prescribe for, or offer advice on cancer. This was because 'Many of the so-called cures for cancer are harmful in themselves, their danger is that they induce the sufferer to postpone proper treatment, and that is literally deadly.'[75]

Pharmacy and Medicines Act 1941

The Medicines and Surgical Appliances (Advertisement) Bill 1936 sought to curb the advertisement of patent medicines. As we have noted, the 1936 Bill had fallen at the first fence. There was good reason for this. The newspaper proprietors, whose finances depended on carrying advertisements for patent medicines, imposed a form of censorship. 'Debates in Parliament, reports of prosecutions and the advocacy of reform [were] rarely publicized', and evil practices persisted.[68] These included offers to diagnose illness by post. 'In one particular case of a cure for loss of hair, investigated by the Advertising Association, three separate samples of hair were sent and the same medicine was received by each patient. The fee was two guineas. One patient was a woman, one a man and the third a dog.'[68] The display of testimonials, pseudo-scientific jargon, extravagant claims, appeals to fear, and financial inducements, were still prevalent. The Pharmacy and Medicines Act 1941 finally succeeded in enacting provisions to regulate the patent medicine trade. The 1941 Act prohibited '(with exceptions) advertisements of articles "in terms which are calculated to lead to the use of that article . . . for the treatment of human beings for any of the following diseases, namely, Bright's disease, cataract, diabetes, epilepsy or fits, glaucoma, locomotor ataxy, paralysis or tuberculosis." ' It also prohibited advertisements for abortifacients. The Act at last required the nature and amount of all active ingredients (but not all ingredients) to be displayed on the label of a medicine. One World War had halted progress in this field; it took a second World War to bring it about.

Control of Penicillin Order No. 731, 1946, and the Penicillin Act 1947

Following its isolation from *Penicillium notatum* in 1940 and its marketing by US companies during the war, penicillin was initially in very short supply, and an Order in 1946 under the Defence Regulations made its sale a criminal offence unless it had been prescribed by a doctor.[76] When the supply of penicillin increased, the Government considered whether it was right to allow penicillin to be 'bought and sold like most other articles in a chemist's shop quite freely and without restriction.'[77] It sought the advice of experts, including Sir Alexander Fleming; they advised that there would be dangers in the unrestricted use of penicillin. 'The most serious of these dangers arises when a patient takes too small a quantity. This sort of amateur treatment causes noxious germs to lose their sensitivity to penicillin, with the result that the patient is likely to succumb to the next attack of any illness which might otherwise have responded to this treatment.'

Drugs Advisory Board Bill 1963

The plight of children born with limb-reduction deformities after exposure to the sedative-hypnotic thalidomide *in utero* led to an inquiry by a committee, chaired by the distinguished physician Lord Cohen of Birkenhead, which recommended the establishment of a Committee on Safety of Drugs, with three sub-committees to deal with toxicity, clinical trials, and adverse reactions. The committee was established in 1963 and was chaired by Sir Derrick Dunlop, who had just retired as Christison Professor of Therapeutics in Edinburgh.

As Maurice Edelman MP emphasized in the House of Commons in 1962, 'The thalidomide tragedy has focussed world-wide attention on the need for stricter and more extensive control in the testing and marketing of drugs. I want to suggest that our own methods of testing and controlling the market in drugs are wholly inadequate and that what is required

is a central drug licensing agency, free from commercial pressure, which will have the power to provide essential safeguards which do not exist today.' In due course, the Drugs Advisory Board Bill setting out such a committee was introduced,[78] but never enacted.

Medicines Act 1968

A report from the Committee on Safety of Drugs, followed by a white paper, led to the Medicines Act 1968, legislation to mitigate the risks of new medicines,[79] a decade after thalidomide had been marketed and six years after the first attempts to legislate. It established the apparatus for licensing medicines, and the criteria that had to be met before a licence could be granted, namely:

'(a) the safety of medicinal products of each description to which the application relates;
(b) the efficacy of medicinal products of each such description for the purposes for which the products are proposed to be administered; and
(c) the quality of medicinal products of each such description, according to the specification and the method or proposed method of manufacture of the products, and the provisions proposed for securing that the products as sold or supplied will be of that quality.'

These remain the guiding principles by which the Licensing Authority—the Minister of Health, the Secretary of State concerned with health in Scotland, and the Minister of Health and Social Services for Northern Ireland—on the advice of a committee of experts, judges whether a medicine can be licensed, under the direction of a Medicines Commission. The Medicines Commission, whose first chairman was Derrick Dunlop, established the Committee on Safety of Medicines, which became the main working regulatory body, assisted by the Medicines Control Agency (MCA). When the MCA merged with the Medical Devices Agency in 2003, the name was changed to the Medicines and Healthcare products Regulatory Agency (MHRA). Then in 2005 the Medicines Commission and the Committee on Safety of Medicines were united as the Commission for Human Medicines (CHM). The regulatory process conducted by the CHM is at arm's length from Government, under administration of the MHRA.

The Medicines Act 1968 requires that a licence (now known as a marketing authorization) should be held in respect of all medicinal products, that is, products used for one or more medicinal purposes, namely:

(a) treating or preventing disease;
(b) diagnosing disease or ascertaining the existence, degree or extent of a physiological condition;
(c) contraception;
(d) inducing anaesthesia;
(e) otherwise preventing or interfering with the normal operation of a physiological function, whether permanently or temporarily, and whether by way of terminating, reducing or postponing, or increasing or accelerating, the operation of that function or in any other way.

The Act, which ran to 136 paragraphs, distinguished between prescription-only medicines (PoMs), those that could be purchased in a pharmacy (Ps), and those that could be sold generally (GSLs). Only doctors, dentists, and veterinary surgeons were allowed to prescribe prescription-only medicines. It also regulated the packaging of medicines, their promotion,

the conduct of pharmacies, and several other matters relating to them. The Act now runs, with amendments, such as the Medicines (Cyanogenetic Substances) Order 1984, to over 200 paragraphs.

Misuse of Drugs Act 1971 and Misuse of Drugs Regulations 1985

The increasing use of lysergide (lysergic acid diethylamide, LSD) and cannabis, and of prescription drugs, including amphetamines, methadone, and barbiturates, made it clear that that Dangerous Drugs Act was inadequate to control the 'drugs problem'.[F] Matters could soon become worse. 'Evil men [saw] a profit in exploiting misuse', the fashion for drugs was changing rapidly, and there was 'a handful of irresponsible medical practitioners.'[80] The Misuse of Drugs Act 1971 set up the Advisory Council on the Misuse of Drugs, replacing the non-statutory Advisory Committee on Drug Dependence, to consider a wide range of matters related to drug misuse and to advise ministers.[81] It revised and extended the schedule of controlled drugs; restricted their importation, exportation, production, possession, and supply; made growing cannabis plants illegal; and set out punishments for permitting premises to be used for producing, supplying, or smoking controlled drugs. The Act, and the Misuse of Drugs Regulations that followed, graded drugs as being of Class A, B, or C, 'broadly according to the harmfulness attributable to a drug when it is misused.'[82] The Regulations divided drugs into five schedules. Schedule 1 drugs, such as lysergide, are not used medically. Schedules 2–4 cover drugs with medicinal uses, but which demand restrictions that are most severe for Schedule 2 drugs, such as diamorphine (heroin), and least severe for Schedule 4 drugs, which include zolpidem and the other so-called 'z-drugs', zopiclone and zotepine. Schedule 5 covers formulations, such as pholcodine linctus, that are so weak that controls are minimal.

Poisons Act 1972

The Poisons Act 1972 established a committee, the Poisons Board, to advise the Secretary of State on the Poisons List.[83] This had been established by the Pharmacy and Poisons Act 1933, which the 1972 Act largely replaced. The Secretary of State also looked to the Poisons Board to recommend or advise on the Poisons Rules, which set out, for example, the ways in which poisons must be bottled or stored. The List distinguished between poisons that could only be sold by a retail pharmacist, and those that could also be sold by a person or business licensed to do so. It did not set out to generally restrict poisons used in the practice of medicine, or the activities of wholesale or export businesses.

Controlled Drugs (Penalties) Act 1985

This Act increased the maximum imprisonment penalty for trafficking Class A drugs from 14 years to life.[84]

[F] Lady Wootton's 1968 report on cannabis had drawn a distinction between cannabis and opiates, and recommended that 'Possession of a small amount of cannabis should not normally be regarded as a serious crime to be punished by imprisonment.' (Bewley T. The illicit drug scene. *Br Med J*. 1975;2(5966):318-320.) That report was not universally welcomed. (Langford-Holt J. Cannabis (Advisory Committee's Report). Hansard 1969; 776: col 661-5.)

1985 Medicinal Products: Prescription by Nurses etc. Act 1992

Since the 1858 Medical Act, the only prescribers who could claim a fee for prescribing had been medical practitioners, and the Medicines Act 1968 restricted the prescription of prescription-only medicines to doctors, dentists, and veterinary surgeons. This Act extended prescribing rights to 'registered nurses, midwives and health visitors.'[85]

The 21st century

Misuse of Drugs Regulations 2001

The Misuse of Drugs Regulations 2001 allow for lawful possession and supply of controlled (illegal) drugs for legitimate purposes.

EU Directives

Between the United Kingdom's accession to the European Economic Community on 1 January 1973 and its exit on 31 December 2020, medicines regulation became increasingly dependent on directives from the European Union, and specifically the European Medicines Agency, of which, at that time, the MHRA was a member.

Regulation (EC) No 726/2004 laid down Community procedures for authorization and supervision of medicinal products for human and veterinary use and established the European Medicines Agency.[86]

Regulation (EC) No. 1394/2007 created a legal framework for advanced therapy medicinal products (gene therapy medicinal products, somatic cell therapy medicinal products, and tissue engineered products).[87]

Regulation (EC) No. 536/2014 introduced a legal requirement for reporting the results of clinical trials, including pharmacological interventions.[88]

Psychoactive Substances Act 2016

The proliferation of 'legal highs'—psychoactive chemicals with structures that differed from those of drugs listed in the Misuse of Drugs Acts—entrained a change in thinking, so that the manufacture, import, and possession of all psychoactive substances were made illegal unless, like caffeine, alcohol, and tobacco, they were exempt or ordinarily taken as food; or if they were intended for healthcare or research.[89]

Medicines and Medical Devices Act 2021

Baroness Cumberlege, in a report titled *First Do No Harm*,[90] described in detail the harms arising from three medical interventions, of which two were medicines—hormones taken as pregnancy tests and the antiepileptic drug sodium valproate. In the light of her investigation, she argued for 'a patient safety commissioner—a voice for, and listener to, patients.'[91] The 2021 Act required the Secretary of State to appoint a Patient Safety Commissioner, whose duty is 'to promote the safety of patients with regard to the use of medicines and medical devices.'[92]

MHRA regulations

Since the MHRA was founded, it has introduced various regulations in response to adverse drug reactions, requiring drug developers to undertake studies necessary for the award of a marketing authorization. Examples include:

- a requirement to study the effects of a medicine in elderly people, following adverse effects of benoxaprofen, including deaths, in elderly people;[93]
- rules about the first use in human of newly developed medicines, following serious adverse effects during first-in-human studies of TGN1412 (now called TAB08).[94]

Contraindications and cautions are also added to the label from time to time when adverse effects become apparent. Examples include:

- restricting the use of aspirin to those over 16 years of age because of the risk of Reye's syndrome;[95] [96]
- adding a warning about the risk of an interaction of repeated doses of paracetamol with warfarin.[97]

In some cases a licence may be revoked if a serious adverse reaction is discovered.[98] Examples include the withdrawal of rofecoxib in 2004 and of lorcaserin in 2020.

Summary

Henry VIII's grant to the Physicians of the right to control the quality of medicines sold by Apothecaries was a manifestation of the tension between protecting the interests of the public by quality assurance and protecting the financial self-interest of special groups. At least the Stamp Acts of the late 18th and early 19th centuries had as their clear objective the financial interest of the State. The persistence of the Stamp Acts over 150 years, despite repeated indications of profiteering and scant evidence of therapeutic benefit for many proprietary remedies that were graced by an official-looking excise stamp, suggested a lack of regard for the public health. Pressure from the Pharmaceutical Society and the British Medical Association, neither of whom was a disinterested observer, led to a Royal Commission, whose far-sighted recommendations were lost in the Great War. Even after the shock of the thalidomide tragedy, several years passed before effective legislation was enacted, and at last specifications were laid down for medicines to be acceptably safe, efficacious, and of good pharmaceutical quality. The Medicines Act 1968 has, with modifications, allowed regulators to operate for over half a century with a largely good record on the provision of safe and effective medicines. When regulation has failed to weed out medicines that have subsequently proved problematic, because of adverse reactions or interactions, the introduction of further regulations have sought to prevent similar problems, as discussed above.

The fear of poisoning, and evidence that murder by poisoning was rife, encouraged successive pieces of legislation to control the sale of poisonous substances. Even then, the enforcement of the Poisons Act 1868 with respect to proprietary medicines was laggardly, and itself a response to the increasing number of inquests into deaths from overdose with chlorodyne, which contained morphine and chloroform.

The tensions between commerce and public safety persist. Data on which licensing decisions are made remain 'commercial-in-confidence'. New legislation, permitting provisional market access without the thorough investigations required for a full marketing authorization, could shift the balance between benefits and harms. As less information will be available when a licensing decision is made, it will make evaluation more uncertain for the patient, but more advantageous for the market authorization holder.

Conclusions

Medicines regulation, which must balance access to effective medicines against the safety of the public, is hard. In England over several centuries legislators have often been slow to protect the public and reactive rather than proactive. Commercial interests have from time to time significantly influenced the shape and enactment of legislation, as have incidental events, such as wars, and serious adverse drug reactions.

Declaration of interests

JKA is a past vice-chairman of the Medicines Commission, and a President Emeritus of the British Pharmacological Society; he is chairman of the British Pharmacopoeia Commission's Joint Expert Advisory Groups on Pharmacy and Nomenclature and a member of the WHO's Expert Advisory Panel on International Pharmacopoeia and Pharmaceutical Preparations. He has written articles on the history of history of drug regulation and legislation.

REF is retired Director of the West Midlands Centre for Adverse Drug Reactions and Yellow Card Centre West Midlands, which received funding from the Medicines and Healthcare products Regulatory Agency (MHRA), and a retired Member of the MHRA's Pharmacovigilance Expert Advisory Committee.

JKA and REF have both written articles and edited textbooks on adverse drug reactions and have acted as an expert witnesses in civil and coroners' cases involving such reactions; they have written articles on drug advertising, medicines regulation, and on the Prevent Future Deaths report of English coroners.

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