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ESSENTIALS Two tragedies created drug regulatory authorities in the form they exist today. The marketing in 1937 of an elixir of sulphanilamide using diethyl alcohol as the solvent led to over 100 children dying from acute kidney injury. The use from 1957 of thalidomide as a treatment for morning sickness led to the development of phocomelia (and other abnormalities) in the fetuses of about 10 000 mothers who had been given it during their pregnancies. Drug regulatory authorities initially tended to be risk averse, but now recognize concern that the process of drug regulation might inhibit the development and licensing of novel products. They now pursue a more risk-based approach to regulation and seek to support safe innovation, with arrangements including scientific advice programmes, orphan drug approval processes, and expedited approval processes, although these are not without their critics.

Regulation of medicines The regulation of medicines started, in a modest way, during the 18th and 19th centuries with the publication of pharmacopoeias intended to ensure the quality of medicinal products sold to the public. These did not specify the purposes for which products should be used, and they were advisory rather than compulsory, although they probably had some impact. The 20th century, however, saw substantial changes arising from a combination of scandal and tragedy. In 1906 the British Medical Association published a slim volume entitled *Secret Remedies: What they Cost and What they Contain*, which was an exposé of the patent medicines industry. Beechams Pills—containing only aloes, powdered ginger, and powdered soap—were promoted for numerous purposes that ranged from ‘constipation’ to ‘maladies of indiscretion’ and even ‘menstrual derangements’, which was interpreted as a covert claim as an abortifacient. The public in both the United States and Britain were horrified. In America, where the US Congress was discussing a ‘Pure Foods Act’, the legislation was extended to medicines, thus creating the Food and Drugs Administration (FDA). In the United Kingdom things moved rather more slowly. After the publication, in 1909, of a sequel entitled *More Secret Remedies*, Parliament established a Select Committee to advise on what measures should be put in place to protect the public. Its report recommended that legislation be enacted to regulate the supply of medicines to the public. Sadly, the Committee published its findings the day before the start of the First World War and it was largely forgotten. Tragedies that shaped drug regulation Two tragedies created drug regulatory authorities in the form they exist

today. In 1937 an American pharmaceutical company, Massengill, began marketing an elixir of sulphanilamide using di-ethyl alcohol as the solvent. Over 100 children died from acute kidney injury as a result of the solvent's nephrotoxicity. As a consequence, the FDA's powers were enhanced, but virtually nothing was done in Europe. In 1957 the German drug company Grünenthal placed thalidomide on the market as a treatment for morning sickness without undertaking any reproductive toxicology tests. It became apparent, after a delay of almost three years, that thalidomide caused phocomelia (malformations of the arms and/or legs), as well as other abnormalities, in the fetuses of mothers who had been given it during their pregnancies. It is estimated that, worldwide, 10 000 babies were afflicted, although the thalidomide disaster was largely avoided in America as a result of the legislative response to the sulphanilamide tragedy. In response to these disasters—particularly the thalidomide tragedy—national drug regulatory authorities were established in almost all countries. They all have legal powers—within their jurisdictions—to ensure that medicines placed on their markets are of good quality, are effective in the uses promoted by their manufacturers, and that they are safe in relation to their efficacy. Within the European Union almost all new drugs are now authorized by the so-called 'centralized procedure' which means that they become licenced, simultaneously, across all 28 member states. The European Medicines Agency (EMA) undertakes a detailed scientific scrutiny of the evidence through its Scientific Committees and makes a recommendation whether or not new products should be granted so-called 'marketing authorization'. Because of their historical origins, drug regulatory authorities initially tended to be risk averse. Although they were not opposed

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186 section 2 Background to medicine to pharmaceutical innovation, there had been some concern that the process of drug regulation might inhibit the development and licensing of novel products. However, regulatory authorities have increasingly recognized that they have an important role in not only protecting public health, but supporting innovation. They have therefore taken considerable steps over recent years to ensure a more risk-based approach to regulation, reducing regulatory burdens where possible, and putting in place measures to support safe innovation. Support for innovation Provision of advice Regulatory agencies have, for many years, offered the sponsors of new products the opportunity to seek scientific advice on the design of their development programmes. At face-to-face meetings, sponsor companies meet with the scientific staff of drug regulatory agencies to discuss their proposed development plans and protocols, including the outcome measures they plan to adopt in demonstrating efficacy. More recently the FDA and EMA have instituted arrangements for the two agencies to provide joint scientific advice. The scientific advice programme is entirely voluntary, with agencies covering their costs by charging fees for the services they offer. The scientific advice that is provided is 'nonbinding' on either party, but nevertheless these scientific advice services are widely used by the sponsors of new products, and few companies would now complete a drug development programme without having sought regulatory advice from the FDA and the EMA or National Authorities in Europe. In the United Kingdom the Medicines and Healthcare Products Regulatory Agency (MHRA) has, in addition to its scientific advice provisions, recently established an Innovation Office. This offers help to all those developing particularly innovative products or techniques/processes, including small and medium-sized enterprises as well as academics who have developed a novel medicine or device, or a novel approach to the development or manufacture of a product. Examples of such innovative products include Advanced Therapy Medicinal Products (cell-based therapies), nanotechnologies, stratified medicines, novel drug/device combinations, and advanced manufacturing techniques.

Orphan drugs In the early 1980s it was recognized, initially in the United States, that manufacturers were being deterred from developing drugs for rare diseases. The development and ongoing costs of such products, to meet the demands of regulation to ensure appropriate standards of quality safety and efficacy, could never be recouped from their sales. The US Congress, in 1983, passed legislation that allowed the US FDA to offer various incentives to sponsors seeking to develop products for rare (so-called 'orphan') diseases. Comparable measures were subsequently introduced in other jurisdictions including the EU, Japan, Singapore, and Australia. In the United States an orphan disease is defined as a condition with less than 200 000 affected persons: in the EU it is defined as a condition with a prevalence of not more than 5 per 10 000 population. To further reduce the burden on manufacturers applying for orphan drug status, the FDA and EMA now use a common application process for both agencies, although each maintains separate approval processes. The orphan drug programme has been an undoubted success. In the EU, for example, more than 100 orphan drugs have been granted marketing authorization since the programme began in 2000. Expedited approval programmes In the mid-2000s, the FDA began to introduce arrangements that would permit promising new products to become more rapidly available to patients. To meet the FDA's requirements for expedited approval, the product must fulfil three criteria. First, the product should be intended to treat a 'serious' condition that has substantial impact on patients' day-to-day functioning. Secondly, the product should expect to be an improvement any 'available therapies' that are approved for the same indication as the new drug. Thirdly, the product should meet 'unmet clinical need', defined as a condition whose treatment is not adequately met by currently available treatments. In the United Kingdom, the MHRA have recently introduced analogous arrangements. A promising innovative medicine designation gives sponsors an indication that a product may be eligible for the Early Access to Medicines Scheme (EAMS) based on early clinical data. Under the scheme, the MHRA provides an opinion on the benefit/risk balance of the medicine based on the data available when the EAMS submission is made. If successful, the MHRA gives a positive opinion that supports prescribers in deciding whether to use the product in patients with life threatening or seriously debilitating conditions before marketing authorization is granted. Discussions are currently taking place with a view to extending the principle of early designation of a promising medicine in Europe. The EMA is currently undertaking a pilot study of the use of 'adaptive pathways' to accelerate the availability of novel products for unmet clinical need. In this scheme a sponsor first targets a narrow indication in an area of high unmet need and subsequently develops the product for broader indications. During the development process input is obtained from other stakeholders such as health technology assessment (HTA) bodies. The scheme is within the existing legislative framework and will likely use provisions such as conditional approval. Once the first approval is granted, the sponsor will then be required to collect additional information about the product's performance in clinical use so that—provided the early promise is fulfilled—full marketing authorization is granted or the indication broadened. Are these mechanisms to support innovation useful? National drug regulatory authorities are clearly making serious efforts to promote the development of safe and effective innovative medicines. In doing so they must continue to balance a product's benefits against its risks, but the approaches that authorities are taking is not without controversy. Some commentators have criticized the arrangements for providing scientific and regulatory advice to companies, whether they be small or large. They believe that doing so will (or has) lead to 'regulatory

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no evidence that this has occurred in either Europe or North America, but the fact that such accusations have been made can leave regulatory authorities feeling—at best—uneasy. The converse is that, without appropriate advice, those developing novel products run the risk of failing to understand what is required of them, undertaking inappropriate or unnecessary studies, and wasting substantial sums of money. Other commentators of a utilitarian persuasion have suggested that (at least in the EU) the orphan drugs legislation should be re-pealed. They argue that their development costs are still very high, even with incentives, and as a consequence the costs of providing patients with orphan products is likely to deprive those with common conditions of cost-effective care. This attitude is countered by egalitarians who claim that society has a duty—within reason—to help those with any condition achieve the quality of life to which they are entitled. There is no substantial appetite at present in the United Kingdom, the European Union, or North America to repeal the orphan drugs arrangement. The arrangements for expedited approval in the United States have also been criticized on two grounds. First, it has been claimed that the number of safety warnings issued after the launch of products undergoing expedited approval have been greater than those approved under conventional approaches. This may well be correct because the data on which expedited approvals are made are likely to be less. Nevertheless, if patients with unmet clinical need are to have access to products that may have a profoundly beneficial effect on their lives, a reduced safety database would seem to be a price worth paying. The second criticism is that the benefits have been limited, at least for some products that have gone through an expedited approval. This has been particularly alleged in respect of some anticancer agents, when approvals for products used in later stages of the disease have been based on intermediate endpoints (such as reductions in tumour size), with only a modest increase in longevity. Despite these criticisms regulatory authorities are continuing to develop arrangements that would allow patients earlier access to promising new products. It is in the best interest of patients and the public that they succeed.

FURTHER READING Carpenter D (2010). Reputation and power: organizational image and pharmaceutical regulation at the FDA. Princeton University Press, Princeton. Emanuel M, et al. (2012). Thalidomide and its sequelae. *Lancet*, 380(9844), 781–3. Stephens MDB (2010). The dawn of drug safety. George Mann Publications, Easton, Winchester.

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