

Thalidomide and its sequelae

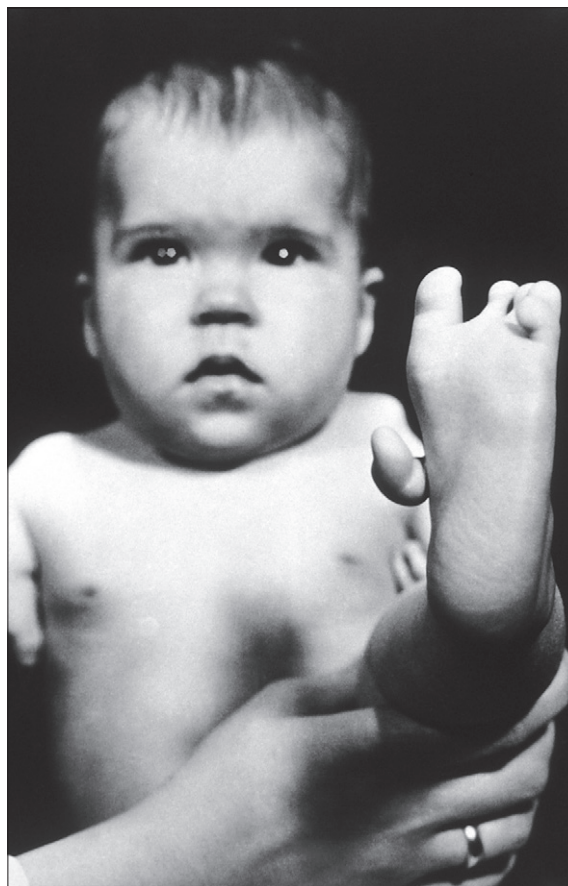
Dec 16, 1961, became one of the most important dates in the calendar of modern therapeutics when *The Lancet* published a letter from W G McBride, an Australian obstetrician, describing the tragedy of congenital abnormalities caused by use of thalidomide in pregnancy.¹ Before this, Widukind Lenz, a German paediatrician, had written to Chemie Grünenthal, the manufacturer of thalidomide, expressing his concerns about the potential of the drug to cause multiple birth defects, and presented his data to a paediatric meeting. On Nov 21, 1961, the company withdrew thalidomide from sale in Germany, but not in other countries.²

Before thalidomide, the only regulation of medicines in the UK was control of the quality of therapeutic substances through their manufacture and supply; there was no requirement for provision of evidence to support claims for either clinical safety or efficacy. Regulation was dominated by a series of Pharmacy Acts, whose purpose was to control the sale of poisons.³ A similar situation pertained in the USA until 1938, when the Federal Food, Drug and Cosmetic Act was amended to include not only a requirement for disclosure of composition and method of preparation of medicines, but also evidence of products' safety.⁴ In 1960, two US senators, Kefauver and Harris, had proposed an amendment to that Act to require that manufacturers also provide proof of efficacy of their products before approval. This amendment made little progress in Congress until the thalidomide issue surfaced. Thalidomide had not received regulatory approval in USA, although it had been licensed in Canada, and thus the USA was largely spared the drug's effects.

Thalidomide had been introduced into an almost unregulated German market in 1957 as an alternative to barbiturates, widely advertised as being safe for everyone "even during pregnancy for mother and child". The fact that it also had antiemetic properties made it even more attractive for morning sickness in the first trimester. Thalidomide was further claimed to be safer than barbiturates in overdose. By the time of its withdrawal at the end of 1961, it was estimated that more than 10 000 children had been born with deformities such as phocomelia as a result of thalidomide use by their mothers.⁵

Even before the crisis precipitated by thalidomide, the UK Government had been concerned about the safety of

marketed medicines. A working party had been set up in 1959 by the Chief Medical Officer, stating in a report in 1962 that "it is a serious defect of the present law that new medicines can be offered for sale and supply with insufficient evidence for their safety". No mention was made in the report about efficacy. The emergence of the thalidomide problem gave greater urgency to the recommendations of the Report and in June, 1962, a new Expert Committee recommended the establishment of an independent advisory board, the Committee on Safety of Drugs (CSD), as an interim measure while more complete legislative reform could be introduced. The role of this committee was to establish the safety of new drugs, to monitor the adverse effects of existing drugs, and to keep medical practitioners informed. The CSD had no mandate for the assessment of efficacy and no statutory powers, depending entirely on the voluntary submission of new products by the pharmaceutical industry. However, the level of cooperation by industry



Science Photo Library

with this voluntary scheme was high, driven in part by the events surrounding thalidomide, but also by a wish to avoid the more rigorous procedures being adopted by the US Food and Drug Administration (FDA).⁶

The European Economic Commission (EEC) was also considering its response to thalidomide, and in 1965 produced a Directive that provided for refusal of marketing authorisation if a product's composition was not as declared, if it was harmful in normal conditions of use, or if evidence of its efficacy was lacking or insufficiently substantiated.⁷ Since this Directive predated UK membership of the EEC, it did not apply in Britain. However, the view was taken that the level of protection of public safety in the UK should not be lower than in the rest of Europe, and in 1968 the UK Parliament passed the Medicines Act, which covered efficacy as well as safety and quality of marketed medicines, recognising that safety can only be assessed in relation to benefit. The Act went beyond the European Directive in the introduction of regulation of clinical trials through a system of clinical trial certificates of approval. The Medicines Act passed into law in the UK in 1972.

The regulatory response to thalidomide was, paradoxically, much faster in the USA than in Europe. The amendments to the Food, Drug and Cosmetic Act proposed by Senators Kefauver and Harris were approved; drugs on the market pre-1962 were reclassified as effective, ineffective, or requiring further study. In addition, adverse drug reactions were required to be reported to the FDA. These requirements were introduced in the USA almost a decade before the UK Medicines Act.⁸

These legislative moves had profound effects on the pharmaceutical industry. Drug testing practices were standardised and clinical research departments were created. Perhaps surprisingly, innovation in the discovery of new drugs was not curtailed, and the 1960s became a golden era for pharmaceutical research and resulted in many of the medicines which are still in widespread use today, for treatment of cardiovascular, central nervous system, and other disorders.⁹

So what is the legacy of thalidomide today? Drug development was formalised into preclinical and clinical phases, and regulatory oversight became more rigorous. With respect to clinical safety, it soon became apparent that the relatively limited patient exposure in clinical trials before marketing did not provide full assurance of

safety in wider clinical practice. In 1963, the chairman of the UK CSD wrote to every member of the medical and dental professions asking them to report untoward conditions that might result from drug treatment. Postmarketing surveillance had arrived. The reports were submitted to the UK Department of Health on yellow cards which are still in use today, albeit in a more sophisticated format. Every other major regulatory authority has evolved similar systems that are used to detect early signals of possible drug toxicity. But this form of passive reporting has drawbacks in under-reporting and an inability to gauge the frequency of an adverse effect. More active forms of surveillance have been created using techniques of pharmacoepidemiology, such as patient registers and clinical databases, which can be interrogated for drug safety problems and which do not rely on doctors notifying regulators. A new name, pharmacovigilance, was coined, denoting the study of the safety of marketed medicines.

Nonetheless, severe drug safety problems continue to occur. Regulation of medicines must follow scientific advances and as new technologies such as genomics become more important in drug discovery, fresh problems arise. In 2006, a humanised monoclonal antibody, TGN 1412, went into early volunteer studies in the UK and produced life-threatening effects that were not predicted from preclinical research. It transpired that the response to TGN 1412 differed greatly across mammalian species, and even responses in primates could not predict the effect of the antibody in human beings. The unpredicted release of cytokines produced in the human volunteers and its disastrous consequences emphasised the difficulties of modelling human responses in animal studies. This landmark case resulted in changes in the way that biological products are developed and regulated, and the way that first-in-man studies with them are undertaken.¹⁰

Less dramatic but equally important were the clinical effects produced by rofecoxib, a non-steroidal anti-inflammatory agent. Rofecoxib's promise was to relieve the pain of arthritis without producing the gastric irritation that is a common adverse effect of anti-inflammatory drugs. Knowledge of the pharmacology of this group of drugs would predict the possibility of increasing the risk of cardiovascular disease, but this risk was downplayed by the manufacturer and underestimated by the regulator, with severe consequences.^{11,12} As a result, the concept of risk management planning arose

whereby regulatory marketing applications now contain a full assessment not only of the known safety issues, but also those that are possible, together with plans for how these would be managed.

Similar considerations apply to the regulation of medical devices. Recent events in this area have drawn attention to the importance of risk management and long-term postmarketing surveillance of quality, effectiveness, and safety. Medical devices must be subject to similar scrutiny as medicines, and as scientific advances lead to more complex devices, regulation must adapt accordingly.¹³

Today, we do not consider drug safety in isolation. As outlined in the Medicines Act many decades ago, the safety of a drug must be considered in relation to the benefits it confers. Assessment of the balance between benefit and risk of a drug and how this can be managed over its lifecycle are the latest preoccupations of drug regulators and the pharmaceutical industry, but whether these tools will be sufficient to prevent newer episodes of major drug induced harm can never be guaranteed. What is certain is that an increasing and central role of drug safety in the science and practice of drug development, combined with robust development of regulatory science, are essential prerequisites to minimise risk.

Michael Emanuel, Michael Rawlins, Gordon Duff,

*Alasdair Breckenridge

Centre for Health, Medicines and Society, Oxford Brookes University, Oxford, UK (ME); National Institute for Health and Clinical Excellence, London, UK (MR); Department of Medicine, University of Sheffield,

Sheffield, UK (GD); and Medicines and Healthcare Products Regulatory Agency, London SW1W 9SZ, UK (AB)
alasdair.breckenridge@mhra.gsi.gov.uk

We declare that we have no conflicts of interest. MR is chairman of the National Institute for Health and Clinical Excellence. GD is chairman of the Commission on Human Medicines. AB is chairman of the Medicines and Healthcare products Regulatory Agency.

- 1 McBride WG. Thalidomide and congenital abnormalities. *Lancet* 1961; **2**: 1358.
- 2 Mann RD. Modern drug use: an enquiry on historical principles. Lancaster: MTP Press, 1984: 606.
- 3 Bartrip P. A "pennurth of arsenic for rat poisoning": the Arsenic Act 1851 and the prevention of secret poisoning. *Med Hist* 1992; **36**: 53–69.
- 4 Dunn JH. Federal Food, Drug and Cosmetic Act. Chicago: Clearinghouse Press, 1938.
- 5 Mann RD. Modern drug use: an enquiry on historical principles. Lancaster: MTP Press, 1984: 598.
- 6 Tansey EM, Catterall PP, Christie DA, Willhoft SV, Reynolds LA, eds. Wellcome witnesses to twentieth century medicine: the Committee on Safety of Drugs. London: The Wellcome Trust, 1997; **1**: 103–32.
- 7 Couve de Murville M. Directive 65/65 EEC. Council Directive of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products. (OJL no 22 of 9.2). 1965: 369.
- 8 Krantz JC Jr. New drugs and the Kefauver-Harris amendment. *J New Drugs* 1966; **6**: 77–79.
- 9 Quirke V. The impact of thalidomide on the British pharmaceutical industry: the case of Imperial Chemical Industries. In: Gaudilliere J-P, Hess V, eds. Ways of regulating: therapeutic agents between plants, shops and consulting rooms. Berlin: Max Planck Institute, 2009; preprint **363**: 125–41.
- 10 Suntharalingam G, Perry MR, Ward S, et al. Cytokine storm in a phase 1 trial of the anti-CD 28 monoclonal antibody TGN 1412. *N Engl J Med* 2006; **355**: 1018–28.
- 11 Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000; **343**: 1520–25.
- 12 Merck. Merck announces voluntary worldwide withdrawal of Vioxx. Sept 30, 2004. http://www.merck.com/newsroom/vioxx/pdf/vioxx_press_release_final.pdf (accessed Aug 1, 2012).
- 13 The Lancet. Stricter devices regulation needed—lessons from the past. *Lancet* 2012; **379**: 2402.

Chronic kidney disease: a coronary heart disease equivalent?



Designation of a disorder as a coronary heart disease risk equivalent would imply that the disorder leads to a 10-year risk of coronary death or myocardial infarction that is at least as high as after myocardial infarction (ie, usually exceeding 20%).¹ Guidelines therefore recommend lipid-lowering therapy (in addition to therapeutic lifestyle changes) for most adults with a coronary heart disease risk equivalent.^{1,2} Evidence points to a strong association between coronary heart disease and chronic kidney disease.³ In *The Lancet*, Marcello Tonelli and colleagues⁴ address a natural question arising from epidemiological data: does

chronic kidney disease constitute a coronary heart disease risk equivalent?

Tonelli and colleagues used data from the Alberta Kidney Disease Network (AKDN) in Canada. The study assessed almost 1.3 million individuals, not on dialysis, with a median follow-up of 48 months. The primary definition of chronic kidney disease was an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 m², estimated with the Chronic Kidney Disease Epidemiological Collaboration equation.⁵

The primary outcome was first admission to hospital for myocardial infarction, ascertained by linking AKDN

Published Online
June 19, 2012
DOI:10.1016/S0140-
6736(12)60772-7
See [Articles](#) page 807