At the end of 1961, the manufacturer withdrew thalidomide. Many years later, after public campaigns and legal action, the victims began to receive compensation. The toll of these devastating abnormalities was immense – across the 46 or so countries where thalidomide was prescribed (in some countries even sold over the counter), thousands of babies were affected. The thalidomide tragedy stunned doctors, the pharmaceutical industry, and patients, and led to a worldwide overhaul of the process of drug development and licensing.[3]

Vioxx

Although drug-testing regulations have been tightened up considerably, even with the very best drug-testing practices there can be no absolute guarantee of safety. Non-steroidal anti-inflammatory drugs (NSAIDs) provide a good illustration of why vigilance in relation to drugs is needed. NSAIDs are commonly used to relieve pain and reduce inflammation in various conditions (for example, arthritis), and also to lower temperature in patients with a fever. The 'traditional' NSAIDs include many drugs that are available over the counter such as aspirin and ibuprofen. Among their side-effects, they are well known for causing irritation of the stomach and gut, leading to dyspepsia ('indigestion') and sometimes bleeding and even gastric (stomach) ulcers. Consequently, there was good reason for drug companies to see if they could develop NSAIDs that did not cause these complications.

Rofecoxib (best known by the marketing name of Vioxx, but also marketed as Ceoxx, and Ceeoxx) was introduced in 1999 as a supposedly safer alternative to the older compounds. It was soon widely prescribed. Little more than five years later Vioxx was withdrawn from the market by the manufacturer because of an increased risk of cardiovascular complications such as heart attack and stroke. So what happened?

Vioxx was approved by the US Food and Drug Administration (FDA) in 1999 for the 'relief of the signs and symptoms of osteoarthritis, for the management of acute pain in adults, and for the treatment of menstrual symptoms [that is, period pains]'. It was later approved for relief of the signs and symptoms of

rheumatoid arthritis in adults and children. During development of Vioxx, drug company scientists became aware of potentially harmful effects on the body's blood clotting mechanisms which could lead to an increased risk of blood clots. Yet the generally small studies submitted to the FDA for approval purposes concentrated on evidence of Vioxx's anti-inflammatory effect and were not designed to look into the possible complications.[4]

Before the FDA approval, the company had already begun a large study mainly designed to compare gut side-effects by comparison with those of another NSAID, naproxen, in patients with rheumatoid arthritis. Once again, the study was not specifically designed to detect cardiovascular complications. Moreover, questions were later raised about conflicts of interest among members of the study's data and safety monitoring board (these boards are charged with monitoring the accumulating results of studies to see whether there is any reason for stopping the research).

Nevertheless, the results – which showed that Vioxx caused fewer episodes of stomach ulcers and gastrointestinal bleeding than naproxen – did reveal a greater number of heart attacks in the Vioxx group. Even so, the study report, published in a major medical journal, was heavily criticized. Among its flaws, the results were analyzed and presented in such a way as to downplay the seriousness of the cardiovascular risks. The journal's editor later complained that the researchers had withheld critical data on these side-effects. However, the results, submitted to the FDA in 2000, and discussed by its Arthritis Advisory Committee in 2001, eventually led the FDA to amend the safety information on Vioxx labelling in 2002 to indicate an increased risk of heart attacks and stroke.

The drug company continued to investigate other uses of Vioxx, and in 2000 embarked on a study to see whether the drug prevented colorectal (lower gut) polyps (small benign tumours that may progress to colorectal cancer). This study, which was stopped early when interim results showed that the drug was associated with an increased risk of cardiovascular complications, led to the manufacturer withdrawing Vioxx from the market in 2004. In the published report, the study's authors, who were either

employed by the manufacturer or in receipt of consulting fees from the company, claimed that the cardiovascular complications only appeared after 18 months of Vioxx use. This claim was based on a flawed analysis and later formally corrected by the journal that published the report.[4] In the face of numerous subsequent legal challenges from patients, the manufacturer continues to claim that it acted responsibly at all times, from pre-approval studies to safety monitoring after Vioxx was marketed. It has also reaffirmed its belief that the evidence will show that pre-existing cardiovascular risk factors, and not Vioxx, were responsible.[5]

The Vioxx scandal shows that, half a century after thalidomide, there is still much to do to ensure that treatments are tested fairly, that the process is transparent, and that the evidence is robust. As one group of commentators put it 'Our system depends on putting patients' interests first. Collaborations between academics, practising doctors, industry, and journals are essential in advancing knowledge and improving the care of patients. Trust is a necessary element of this partnership, but the recent events have made it necessary to institute proper systems that protect the interests of patients. A renewed commitment by all those involved and the institution of these systems are the only way to extract something positive from this unfortunate affair'.[4]

Avandia

2010 saw another drug – rosiglitazone, better known by the trade name Avandia – hitting the headlines because of unwanted side-effects involving the cardiovascular system. Ten years earlier Avandia had been licensed by drug regulators in Europe and the USA as a new approach to the treatment of type 2 diabetes. This form of diabetes occurs when the body does not produce enough insulin, or when the body's cells do not react to insulin. It is far more common than type 1 diabetes, in which the body does not produce insulin at all. Type 2 diabetes, which is often associated with obesity, can usually be treated satisfactorily by modifying the diet, exercising, and taking drugs by mouth rather than by injecting insulin. The long-term complications of type 2 diabetes include an increased risk of heart attacks and strokes; the main aim of treatments is to reduce the risk of these complications.