



THE THALIDOMIDE TRAGEDY

- Offprint -

Extract from the German jubilee publication

“Unser Weg 1946-2006: 60 Jahre Grünenthal GmbH”



THE THALIDOMIDE TRAGEDY

- Offprint -

IMPRINT

Editors: Grünenthal GmbH, Aachen 2007 **Cover picture:** Grünenthal GmbH, Aachen

Author: Dr. Helmuth Bischoff, MIC-GmbH Heidelberg **Editorial Management:** Dr. Annette

Fusenig, Grünenthal **Print:** Druckerei Theo Peters, Herzogenrath

Thalidomide – the active ingredient of an hypnotic agent which was sold in Germany under the trademark Contergan – triggered a global tragedy. This tragedy is and remains part of the corporate history of Grünenthal. Even now, after almost 50 years, it remains a difficult topic. The remarks that follow are intended to present an account of different aspects of this story.

The suffering experienced by people who took thalidomide during the period from 1957 to 1961 is incalculable. The reported number of those harmed varies, but more recent scientific studies indicate that 10,000 people worldwide were affected. Germany accounted for half of that number. Of the some 5,000 German thalidomide victims, 2,800 are still alive today.

There had never before been such a major tragedy related to a medicinal product. How did it come about?

Thalidomide was developed by Grünenthal in 1954. The substance had a sedative effect and was used to promote sleep. Unlike other hypnotics of that period it was not associated with dependency and it appeared to be particularly well tolerated. In line with the pharmacological and toxicological investigations carried out in rodents – standard practice at that time – the product was subjected to the usual battery of investigations. These revealed no signs of any risk whatsoever. And because in the mid-1950s there were no guidelines for the development, production and marketing of medicinal products, no uniform federal medicines act, and no licensing authority such as the present Federal Institute for Drugs and Medical Devices (BfArM), it was possible to introduce the hypnotic agent manufactured on the basis of thalidomide on the German market on 1 October 1957 without any governmental review of the documentation. At that time testing for harmful teratogenic effects was not standard practice and was in no way indicated.

Thalidomide rapidly became the top-selling hypnotic and sedative in Germany and also achieved large sales internationally under other brand names.

There was general bewilderment in Germany when in 1958/1959 a significant increase was recorded in the numbers of newborn babies with congenital deformities. To begin with, nobody suspected that medication with thalidomide during pregnancy had resulted in these deformities. Public

The tragedy: a historical reconstruction

speculation linked the increased number of deformed babies to nuclear weapons testing in the atmosphere. The German Research Foundation (DFG) initiated a major project to investigate this matter. In September 1959 the Department of Health of the Federal Ministry for the Interior ratified the establishment of a "Working Party on matters relating to genetics, in particular to the incidence and causes of deformity and to radiation damage". It was not until 1961, when all the talk in German hospitals was of 'a deformity epidemic', that research initiatives were set up in five German cities. In Münster, Hamburg, Marburg, Bonn and Kiel systematic efforts were undertaken to identify the cause of this 'epidemic'.

It was also in the autumn of 1961 that Widukind Lenz, a Hamburg-based paediatrician and university lecturer in human genetics, embarked on the first surveys to investigate his suspicion that thalidomide products might possess a teratogenic (defect-causing) effect. On 15 November 1961 he communicated his observations and concerns to the then Head of Research at Grünenthal and backed up this suspicion on the following day in a letter to the company's board of management. At about the same time, identical suspicions were being voiced independently by the Australian gynaecologist Dr. William G. McBride. On 27 November 1961 Grünenthal withdrew its thalidomide products from the market, 12 days after receiving notification of the first plausible suspicions.

It was not until 1964, three years after market withdrawal, that proof of the teratogenic effect of thalidomide was obtained in animal experiments conducted in New Zealand white rabbits. With the laboratory animals routinely used before that time it had not been possible to produce such proof. Only much later did the research community come to realise that humans are about 100 times more sensitive than rodents to the effects of thalidomide. Not least, the thalidomide tragedy yielded the insight that substances found initially to be tolerated in the standard animal tests at that time might still have devastating effects in humans.

A second harmful effect caused by thalidomide was polyneuritis. Multiple instances of this harmful neurological effect following long-term medication with thalidomide became known to Grünenthal in 1960. Once the irreversibility of such effects could not be ruled out, the company applied for prescription-only status for thalidomide in 1961.

One of the most important lessons to be drawn from the thalidomide tragedy was the creation of a wide range of measures to ensure risk minimisation in connection with the licensing of newly developed pharmaceutical products. For Germany, the Medicines Act of 1976, which came into force on 1 January 1978, was a landmark event in this context. Despite global efforts to improve pharmaceutical products, the risk of unknown adverse effects cannot be entirely ruled out even today.

The thalidomide tragedy not only highlighted many deficiencies in pharmaceutical legislation, but also brought about a lasting re-think in terms of policy. Following an amendment to the Medicines Act of the Federal Republic of Germany in 1964, the comprehensive Medicines Act of 1976 was intended to be an 'outstanding social consequence of the Contergan catastrophe'. This Act made it compulsory for new medicines to undergo a stringent licensing and assessment procedure. Since that time companies have had to submit to the regulatory authorities extensive experimental results confirming the efficacy, safety and sufficient quality of medicinal products before a medicine can be licensed for sale for the first time. Special tests to detect any risk of malformation have become standard practice.

As far as Grünenthal was concerned the thalidomide tragedy called into question the continued survival of the company. During the period from 1961 to 1971 virtually all the energies of corporate management were absorbed in preparing for and dealing with the legal proceedings, which took place between 1968 and 1970.

Legal proceedings were instituted against senior managers from 27 May 1968 until 18 December 1970 in Alsdorf near Aachen. Their purpose was to establish whether Grünenthal employees were to blame for the tragedy. The proceedings were closed in December 1970 at the request of the district attorney's office with a judgement of minor fault on the part of the defendants.

The proceedings, which were held before the Grand Criminal Court of the Landgericht Aachen, became the longest and most costly case in German legal history up to that time. Having reviewed all the charges, the court closed the proceedings with a judgement of minor fault. However, it did find that the defendants had acted incorrectly in dealing with the harmful neuro-

The consequences: a comprehensive Medicines Act and support for the victims

The court case 1968 - 1970

logical effects caused by the product. At the same time, however, it recognised that the employees of Grünenthal had adequately tested the sedative and hypnotic drug in accordance with the guidelines then in force. Moreover, the rapid withdrawal of the product from the market was viewed in emphatically positive terms. After the first detailed, justified suspicion that thalidomide might be responsible for producing deformities in the unborn child, Grünenthal had reacted within 12 days and had withdrawn its thalidomide products from the market in November 1961.

Even before the end of the legal proceedings, a settlement was agreed in April 1970 under the terms of which Grünenthal undertook to pay DM 100 million to the thalidomide victims. This settlement took the company to the brink of financial ruin. The amount of compensation agreed at that time was about DM 20 million higher than that certified by neutral appraisers to be the maximum, economically justifiable burden for Grünenthal.

The government also acknowledged its responsibility and looked for ways to compensate the victims appropriately. Consequently, a Foundation Act was introduced and the 'Hilfswerk für behinderte Kinder' ['Aid for Disabled Children'] foundation regulated by public law was established. The sum of DM 100 million plus DM 10 million interest was donated by Grünenthal to this foundation, set up in 1972, and the German government contributed a further DM 100 million. From this foundation the victims still receive a monthly pension, the level of which varies depending on the degree of disability. As of December 2005 more than € 400 million have been paid out in this way.

Legal cases instituted up to the mid-1980s against the foundation solution were dismissed. The constitutional conformity of the legal solution was confirmed.

Handling data and facts

In seeking to understand public reactions to and discussions surrounding thalidomide, several levels can be distinguished. The legal judgement given in this case should be a decisive factor here. And of course the statements of those directly affected are of major relevance. As organs of information and opinion-formers, the media need to be considered in two ways: firstly as mass media, and secondly as specialist media in the fields of medicine and pharmacy. Finally, the response of the medical community needs to be considered.

This indicates whether thalidomide led to a general loss of faith vis-à-vis Grünenthal and the medicines it markets or whether the vast majority of doctors retained their faith in Grünenthal products.

While the court found that the employees of Grünenthal had adequately tested the sedative and hypnotic agent in accordance with the non-legally binding rules of the scientific expert societies generally recognised at the time and while it gave an emphatically positive assessment of the prompt market withdrawal of thalidomide, the mass media consistently maintained the opposite view.

The specialist press reacted differently. It largely dispensed with reproaches aimed at Grünenthal and, from the early 1960s onwards, devoted itself instead to a discussion of the new post-thalidomide principles that were intended to improve the previously deficient legislation governing medicinal products. From the mid-1960s onwards the specialist media also started to talk about the active agent thalidomide in a new way. Researchers had again begun to focus attention on the outcast drug following reports from Israel in 1964 of therapeutic successes achieved with thalidomide in leprosy patients. In the interim it has been demonstrated that thalidomide interferes with the development of new blood vessels, a finding that has prompted discussion that the product could have a role to play in cancer therapy. It is reported to prevent the growth of malignant tissue and to deprive tumours of nutrients.

Finally, the response of the medical profession to thalidomide should be regarded as – to some extent – telling. In 1961 Grünenthal was a middle-ranking company with 1,200 employees. After 1961, if doctors in Germany had believed that the company and its employees had been guilty of negligence and if they had avoided using Grünenthal's medicines, this would have spelt the end for the family-owned company. The opposite turned out to be the case: despite the mounting number of thalidomide-related problems in the 1960s, the medical profession has continued to keep faith with Grünenthal products.

Even today, in spite of the improvements achieved in the marketing approval process for pharmaceutical products and in spite of all the judgements of the courts and the compensation schemes implemented, some sectors of the media still misrepresent or twist the historical facts. The present board of management sees its task as to counter false allegations and, beyond that, to make itself available for a fair dialogue on this subject.



www.grunenthal.com