

History of Orphan Drug Regulation—United States and Beyond

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The US Orphan Drug Act, passed in 1982, was the first orphan drug legislation in the world. It is a law based on economic incentives making it financially possible for pharmaceutical firms to develop products for small patient populations. Since passage, many additional countries have developed orphan drug programs and many pharmaceutical firms have developed around the orphan program. Today, more than 500 drugs for rare diseases have been developed in the United States.

The year was 1962. Women in Europe were delivering babies with strange malformations—phocomelia—shortened, flipper-like or absent limbs. In the United States, a very astute medical scientist at the US Food and Drug Administration, Frances O. Kelsey, MD, PhD, was concerned the drug, thalidomide, was not safe for humans preventing its approval in the United States. In Europe, thalidomide was being used as a sleep aid during the first trimester of pregnancy. As a consequence of this alarming situation, the Kefauver–Harris amendments¹ to the Food, Drug, and Cosmetic Act were passed. These amendments, for the first time, required drug manufacturers (sponsors) to prove the effectiveness of their drug product for its intended use prior to the US Food and Drug Administration approval and marketing and to report any serious side effects. The law required that evidence of effectiveness be based on adequate and well-controlled clinical studies conducted by qualified experts. Although the US drug market was rendered safer by the Kefauver–Harris amendments by virtue of a greater degree of study into efficacy; the cost of drug development was significantly increased. Patients with uncommon diseases did not see research into the development of products to treat their diseases. Their diseases went without treatment.

Responding to the increasing inequity experienced by patients with more common diseases vs. patients with less common—rare—diseases, in 1978, the then Department of Health Education and Welfare formed a committee to study the experience encountered by patients with these uncommon diseases.² This multidisciplinary group of individuals selected from the private and government sectors reviewed the situation in great detail issuing a report in 1979 entitled “Significant Drugs of Limited

Commercial Value.” The report established the groundwork for the contents of the 1983 Orphan Drug Act. It concluded that many significant drugs essential for diagnosis or treatment were not being developed because the cost of research and development was not felt to be warranted because of the limited return on investment anticipated from these products.²

It was recognized at the time the report was issued, that the time was right for intervention on the part of government and industry to address the lack of development of drugs for uncommon, also known as presumed unprofitable drugs. Thus, mechanisms mainly based on economic incentives for the development of products needed by rare disease patients, despite the presumed low return on investment for these drugs, were proposed. In addition to the 1979 report, there had been prior reports by such groups as the Office of Technology Assessment (1977), the Commission for the Control of Huntington’s Disease and Its Consequences, and an appeal in 1977 by the White House professional health staff to the Pharmaceutical Manufacturers Association (now the Pharmaceutical Manufacturers and Research Association). Each of these groups expressed concern with the lack of development of drug products for patients with uncommon often serious diseases whose needs were not being addressed. In addition, there were congressional hearings and inquiry from the Secretary of Department of Health Education and Welfare to the US Food and Drug Administration referencing the issue, and there was an increasing number of articles in both the lay and health-related press critical of the lack of concerted action on the part of the government or private industry. Such was the situation for patients in the late 1970s and early 1980s.

At about the same period, two events occurred. The National Organization for Rare Disorders was formed. National Organization for Rare Disorders, still very active today on behalf of patients with rare diseases, garnered the support of the rare disease community and the medical community on behalf of patients. At the same time, Jack Klugman, a well-known television actor on the show *Quincy* featured a story about a young man whose medication was confiscated on the Canadian/United States border as he was bringing an unapproved drug into the

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United States. The young man suffered from a rare disease and the drug in question was approved in Canada. Both Klugman and the young man with the rare disease testified before the US Congress.

In 1982, the US Congress passed the first Orphan Drug Act in the world. It was almost vetoed by then President Reagan fearful the tax incentives would be a budget breaker. However, on January 4, 1983, after intense lobbying by the National Organization for Rare Disorders and other interest groups, it was signed into law. The law contained economic incentives for drug developers to garner a greater return on their drug research and development investment. It was amended three times, first in 1984 to provide a prevalence number of patients with a disease in the United States. Two hundred thousand patients was the number determined based on the prevalence of a number of diseases in which drugs seemed to be promising but companies were not interested in developing the therapies. Also included were tax credits, a grants program for clinical development of a drug, protocol assistance in drug development, and the provision that an orphan drug could be either patentable or not patentable. Interest by the industry began to take off.

The first Orphan drug to be approved under the new law was Hematin (approved in 1984) for acute intermittent porphyria. Acute intermittent porphyria has a prevalence of 10,000–15,000 patients in the United States. Although the disease has serious consequences for patients, the population was so small that incentives were needed to create sufficient interest on the part of a pharmaceutical company in developing a therapeutic for the disease. With assistance from the incentives of the Orphan Drug Amendments to the Food Drug and Cosmetic Act, Hematin was developed.

During the early years of the Orphan Drug program, interest on the part of the pharmaceutical industry was at best, tepid. However, researchers and academics with ideas for therapies were excited and new companies grew around the orphan drug program. Genentech, Genzyme, and BioMarin all grew in large part because of the incentives provided by the Orphan products program. At about the same time, biotechnology-derived products were beginning to be developed. These products were difficult or impossible to patent with a product matter patent, as the principal molecular features of these molecules had been described and published years earlier and thus were in the public domain. An example would be erythropoietin, first developed for chronic kidney failure when the population was <200,000 in the United States. The 7-year exclusivity, an incentive offered by the Orphan Drug Act was extremely important to Amgen, the

company developing it (private conversation with George B. Rathmann, founder.)

As knowledge concerning the opportunities available for the development of drugs for rare diseases became better known, more products were developed and it became apparent that rare diseases were almost always severe and life-threatening. These rare diseases, often genetic, also affected children in large numbers.

It was not until 1999 that the European Union (EU) passed Regulation (EC) No. 141/2000, establishing the EU Orphan Drug Program. Some of the differences in the EU regulation from the United States included a ratio for prevalence of 5/10,000 in the population. The EU was comprised of 15 member states in 1999. That number and the EU census have grown since 1999 and are currently 28 member states, with a population of over 500 million. Hence, a ratio for prevalence was appropriate. The EU does not have across the board tax credits for orphan product development; tax credits are handled on a member state by member state basis. The exclusivity period in the EU is also different from that of the United States. A pharmaceutical sponsor of an approved EU orphan drug is entitled to 6 years exclusivity, with an additional 4 years if the exclusivity is not challenged at the end of 6 years. The EU regulation has been popular with large, medium, and small size pharmaceutical firms. Then there are also programs in other parts of the world: Japan in 1993, Australia in 1998, and others, including Taiwan, Turkey, the Philippines, and beyond.

Thirty-four years have passed since the passage of the US Orphan Drug Act. More than 500 drugs have been approved for marketing by the US Food and Drug Administration for the treatment of rare/orphan diseases. Countless numbers of patients and their families have been provided needed therapies with the assistance of the economic incentives of the program. The program has been implemented in some way in many parts of the world. Many “cutting edge” therapies have seen their first approvals as a result of the US Orphan Drug Act. In speaking with the original framers of the Act, it has been significantly more successful than ever imagined.

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