US Regulatory Response to Thalidomide (1950-2000)

Thalidomide, a drug capable of causing fetal abnormalities (teratogen), has caused greater than ten thousand birth defects worldwide since its introduction to the market as a pharmaceutical agent. Prior to discovering thalidomide's teratogenic effects in the early 1960s, the US Food and Drug Administration (FDA) did not place regulations on drug approval or monitoring as it later did. By 1962, approximately 20,000 patients in the US had taken thalidomide as part of an unregulated clinical trial before any actions were taken to stop thalidomide's distribution. Due to thalidomide's effects on fetuses, both nationally and abroad, the US Congress passed the 1962 Kefauver-Harris Amendments to the 1938 Food, Drug, and Cosmetic Act. These amendments imposed guidelines for the process of drug approval in the US and required that a drug be safe as well as effective before it could be approved and marketed. Thalidomide also influenced the FDA's creation of pregnancy categories; a ranking of drugs based on their effects on reproduction and pregnancy. Thalidomide motivated the laws on regulating and monitoring drugs developed in the US and by the FDA in the twentieth and twenty-first centuries.

Ciba, a pharmaceutical company based in Switzerland, first synthesized thalidomide, a sedative similar to barbiturates and derived from glutamic acid, in 1953. Ciba said that it intended to use thalidomide as an anticonvulsive agent, but when the sedative did not show the desired effect on tested lab animals, Ciba stopped its thalidomide research. In October 1957, Wilhelm Kunz of the West German pharmaceutical company Chemie Grünenthal reexamined the compound and found that thalidomide worked as a sleep aid with no apparent side effects or maximum dose. Thalidomide became a popular sleeping pill in West Germany and was sold under the trade name Contergan.

Combined with aspirin, thalidomide was used to treat everything from colds and coughs to asthma and nervousness. Some claimed that thalidomide could help treat loss of vision (macular degeneration), diabetes, autoimmune diseases, and even some forms of cancer. Some recommended a liquid form of thalidomide to calm children. By the late 1950s, thalidomide was marketed in forty-six countries with sales almost as high as those of aspirin. Around this time research indicated that thalidomide relieved morning sickness in pregnant women. Some doctors recommended the off-label use of thalidomide to pregnant women, and soon this recommendation was generalized to pregnant women in forty-eight countries.

In 1960, a number of reports of nerve inflammation (peripheral neuritis) associated with long-term use of thalidomide surfaced in German medical journals. In early 1961, the pediatrician Widukind Lenz in Germany noticed thalidomide's teratogenic effects and later hypothesized that prenatal exposure to thalidomide caused severe malformations in newborns. Based on initial questionnaires sent to the parents of deformed infants and their physicians, Lenz noticed that approximately twenty percent of the mothers surveyed had taken thalidomide during pregnancy. Lenz then asked all of the parents specifically about thalidomide, and half of them reported using the drug.

On 15 November 1961, Lenz reported his findings and suspicion of thalidomide's teratogenicity to Chemie Grünenthal, and at a pediatric meeting on 20 November, he announced his suspicion. Independent of Lenz's hypothesis, obstetrician William McBride, working in Australia, noticed severe birth defects in the babies whose mothers had taken thalidomide during gestation. The most common birth defects included shortened, absent, or extra arms or legs (dysmelia), incomplete development of extremities (bone hypoplasticity), and a variety of ear, heart, and internal organ defects. In 1961 McBride reported his findings to Distillers Company Limited laboratories, headquartered in Edinburgh, Scotland, the company that produced thalidomide for the UK. Within the few years after thalidomide was first marketed, greater than 10,000 babies worldwide were born with birth

defects attributed to thalidomide. By March 1962 many countries had banned thalidomide.

In 1960, the limited liability corporation Richardson-Merrell applied to the US FDA, headquartered in Maryland, for approval to sell Kevadon, the company's trade name for thalidomide. The company hoped to approve thalidomide as an over-the-counter drug and recommended it to treat a variety of ailments including alcoholism, anorexia, asthma, cancer, poor schoolwork, premature ejaculation, and tuberculosis. The application went to Frances Kelsey, a physician and pharmacologist at the FDA. Kelsey noticed reports of thalidomide's adverse effects in Germany. Because one of thalidomide's recommended uses was treating morning sickness, Kelsey requested more data from Richardson-Merrell to show that thalidomide was safe for use during pregnancy.

At the same time that Kelsey requested more information, the Democratic Senator from Tenessee Estes Kefauver was independently conducting an investigation of the drug industry in the US. As part of his investigation, Kefauver introduced a bill to enhance safety regulations of drugs. Kefauver learned about thalidomide's effects abroad through the work of Helen B. Taussig, a John Hopkins University, Baltimore, Maryland, professor and pediatric cardiologist. In a 1962 Scientific American article, ”The Thalidomide Syndrome,” Taussig narrates the discovery of thalidomide's embryotoxicity and the drug's journey from original synthesis to its widespread distribution. In the article, Taussig writes of the seemingly sudden outbreak of deformities and questions the efficacy of drug testing and distribution. She notes that she was convinced that US regulatory systems would have approved thalidomide for widespread distribution. At the end of the article, Taussig discusses the evolution of drug advertisements and the leniency of governmental regulation in regard to pharmaceutical companies.

In July 1962, Kefauver alerted the press of thalidomide's teratogenic effects to revive his bill, which he later claimed was losing momentum in Congress. Many public figures expressed shock and outrage when they learned that during thalidomide's period of pending approval, Richardson-Merrell had already distributed greater than 2.5 million thalidomide tablets to over 1,200 physicians, who in turn gave them to approximately 20,000 patients in clinical trials. At least 207 of these patients were pregnant at the time of taking thalidomide seventeen of whom later reported having deformed infants.

From these events, the public scrutinized the FDA's policies and methods for drugs. The thalidomide tragedy, as many call it, galvanized Congress into passing the 1962 Kefauver-Harris Amendments to the 1938 Food, Drug, and Cosmetic Act, hereafter called the 1962 Amendments. The 1962 Amendments went into effect on 7 February 1963 and required that for any sponsor of a drug, usually a company, that planned to investigate that drug clinically, that sponsor had to provide the FDA with a detailed outline of the study. The amendments meant that information concerning preclinical studies, the number and qualifications of the clinical investigators, and the nature of the study, were a required feature of these outlines. The sponsor also had to monitor the progress of the studies and continually report its findings to the FDA. All clinical investigators had to sign contracts agreeing to keep adequate records of receipts of drugs and name of persons to whom the drugs were given.

Before the thalidomide saga and the 1962 Amendments, there were scant federal regulations in US for approval or monitoring of clinical trials. No laws required physicians to keep logs of the drugs they prescribed, nor were the physicians required to follow-up with their patients. The 1962 Amendments required that drug manufacturers prove not only the safety but also the efficacy of the drugs distributed on the US market. The original Food, Drug, and Cosmetic Act only required that a new drug be safe. The Amendments also mandated that the FDA had to approve a new drug application before the developing company could publicize the product. Prior to the 1962 Amendments, if the FDA did not disapprove a drug application within six months, then the drug would be automatically approved within the subsequent sixty days. Before these amendments, the FDA approved an average of 46.2 new single drug entities annually. In the decade after, that number dropped to 15.7. The Amendments gave the FDA more power than it previously had to regulate drug manufacturers.

The 1962 Amendments received criticism, however. Opponents claimed that the Amendments prevented the development of chemical compounds and drug development in general. They also argued that the new efficacy requirement resulted in higher drug prices; with more checkpoints to pass

before reaching approval, a greater deal of research and development costs had to be invested into each drug. Many also advocated for patient autonomy, claiming that whether or not to use a drug was a personal choice—a choice that the government shouldn't deny as long as the drug was safe.

In the mid-1960s, thalidomide research continued. In 1965, physician Jacob Sheskin, working in Israel, used thalidomide as a sedative for patients suffering from erytherma nodosum leprosum lesions, an inflammatory complication associated with leprosy that affects about 100 to 200 people in the US annually. In addition to being an effective sedative, thalidomide also augments immune responses to pathogens in people who take it. Experts from a variety of disciplines recognized thalidomide's potential in treating immunological, rheumatologic, hematologic, and oncologic disorders. Some argued that the drug would help treat throat and oral ulcers in patients infected with human immunodeficiency virus (HIV) and that it would help counteract the massive weight loss associated with Acquired Immune Deficiency Syndrome (AIDS). Studies found that more than half of patients with these throat and oral ulcers had completely healed after four weeks of using thalidomide, and almost ninety percent had partially healed.

In 1975, the FDA approved thalidomide to treat leprosy under limited conditions. With many medical subdisciplines requesting permission to test and use thalidomide, the FDA formed a Thalidomide Working Group in 1994 to develop consent forms and patient information brochures. In 1995, the FDA met with pharmaceutical companies that wanted to apply for approval to market thalidomide. Biomedical researchers wanted to test thalidomide's efficacy in clinical trials on conditions such as AIDS wasting syndrome. Furthermore, AIDS activists, who often didn't want to wait for trial results, lobbied the FDA to allow AIDS patients to use the drug.

The FDA allowed marketing of thalidomide by Celgene Inc., a New Jersey pharmaceutical company on 16 July 1998. Together, Celgene and the FDA developed the System for Thalidomide Education and Prescribing Safety (STEPS) program. This program required registration by physicians who prescribed thalidomide, as well as their patients. The program also insisted on a number of contraceptive measures such as proof of an initial negative pregnancy test prior to treatment, proof that the patient was using two forms of contraception, and submission of monthly pregnancy tests. The FDA placed Thalidomide under Category X of the FDA's pregnancy ratings, categories created in 1975 for pharmaceutical companies to label medications according to their affects on reproduction. The fifth and most severe rating, Category X, is for drugs that empirically contribute to fetal deformities, and for drugs whose risks or undesired effects outweigh possible benefits to the patient. This pregnancy rating and the STEPS program later served as a foundation for the FDA's response to isotretinoin (Accutane), a prescription drug used to treat severe acne. Like thalidomide, isotretinoin caused severe birth defects and prompted its manufacturer and the FDA to create a risk management program to prevent fetal exposure.

In July 1998, the FDA approved the marketing of thalidomide, and today the drug is used to treat inflammation associated with leprosy and also acts as a chemotherapeutic agent for patients with cancer of the plasma cells in bone marrow (multiple myeloma). Thalidomide is available through the US Public Health Service Commissioned Corps, headquartered in Washington, DC.

While thalidomide prompted the US government to extend the powers of the FDA with respect to drug approval and monitoring powers, amendments subsequent to those in 1962 have further extended the FDA's system of regulation. In 1976 amendments to the Medical Device Regulation Act required medical device manufacturers to register with the FDA and follow quality control guidelines. Similarly, the 1990 Nutrition Labeling and Education Act required all packaged foods to contain standardized nutritional information and standardized information on serving sizes.

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