SURVEY OF QUALITY REGULATIONS AND STANDARDS

CLASSROOM ACTIVITY: FRANCES KELSEY AND THALIDOMIDE IN THE UNITED STATES: A CASE STUDY RELATING TO PHARMACEUTICAL REGULATIONS

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NOTES TO THE INSTRUCTOR

The regulation of pharmaceutical/medical products raises a number of significant questions. Should AIDS patients be able to obtain drugs that have not been fully tested for safety or efficacy? Should herbal/nutritional supplements be regulated by the government? How does society balance the potential benefit of new pharmaceuticals against their potential risk? What are the responsibilities of companies to ensure the safety of drugs? This case study explores some of these topical issues through a discussion of a pivotal episode in the history of drug regulation in the United States.

In the early 1960s, Dr. Frances Kelsey and her colleagues at the Food and Drug Administration refused to approve the sedative, thalidomide, for use in the U.S.. Thalidomide was later found to cause severe birth defects when taken by pregnant women in Germany, England, and many other countries. This dramatic case captures students’ interest and provides an effective springboard for discussion of pharmaceutical regulation and related scientific, societal, and ethical issues.

We have used this case study with beginning technical college students who are preparing for laboratory careers in biotechnology. We anticipate that this material would be quite appropriate for high school students as well. It has been effective in our classroom to have the students read up to Questions 1 and 2, at the end of the section entitled “The Beginning of the Thalidomide Story.” After discussion, the class votes on whether they would have approved the drug, based on its use in Germany and its supposed safety record there. The students also list on the blackboard what scientific studies they think might adequately demonstrate the safety of a drug. This seems to be an effective way to get the students engaged in the story and discussions of later questions have been spirited. We use a two hour block of time and do not get to all the questions, but some are assigned as homework.

PURPOSE

This dramatic case study tells the story of Dr. Frances Kelsey of the Food and Drug Administration (FDA) and the drug thalidomide. This incident provides a good introduction to the processes by which drugs are approved and regulated in the United States, and the reasons for these processes. This is also a great story showing how the actions of individuals can be important.

BACKGROUND RELATING TO PHARMACEUTICAL REGULATION

When you reach into your medicine cabinet for a bottle of aspirin, you probably assume that the bottle indeed contains aspirin and that taking a couple of tablets will not lead to your untimely death. We take for granted that pharmaceuticals are properly manufactured, labeled, and tested for safety. We can reasonably have this level of confidence in pharmaceuticals because the production of medical products
is stringently regulated and controlled by the federal government. However, this was not always the case; the quality of drugs and foods was virtually unregulated until the early 1900s. Around that time, a major industry emerged to process foods for urban consumers. This burgeoning food industry was filthy and badly managed. There were various efforts to regulate food processing, however, no legislation was passed until 1906. At that time, Upton Sinclair published the novel, “The Jungle,” which graphically described the alarming practices in the food industry. People were so outraged by Sinclair’s descriptions that Congress passed a law to help regulate the production of food and, at the same time, drugs. This law was the original Food Drug and Cosmetic Act (FDCA). In 1927 a separate law enforcement agency, eventually named the Food and Drug Administration (FDA), was formed to enforce food and drug laws.

The 1906 FDCA authorized regulations ensuring that manufacturers did not adulterate or mislabel products, but did not deal with the safety or effectiveness of drugs. An attempt to license drug manufacturers was introduced into Congress in the early 1930s, but the pharmaceutical industry vigorously combated its passage, and legislation to strengthen drug regulation languished.

It finally took a tragic incident to convince the country of the need for new drug safety legislation. Sulfanilamide, an antibiotic, was introduced in the 1930s (Young 1983). Sulfanilamide has the disadvantage of being relatively insoluble and therefore was only available in a pill form making it difficult to administer to children. To obtain a soluble form of the drug, in 1937, a chemist at the S.E. Massengill Company dissolved sulfanilamide in the toxic industrial solvent, diethylene glycol. Many children were treated with the toxic preparation resulting in at least 358 poisonings and 107 deaths. Under the drug laws at that time, a company had no obligation to prove that their drug was safe; therefore Massengill was not held responsible for the deaths. (The company was, however, fined $500 for labeling the drug an “elixir” when it did not contain alcohol.) In response to this tragic incident, drug reform became popular and a revised FDCA was passed in 1938. This law contained the critical provision requiring that manufacturers prove the safety of new drugs with animal and clinical studies.

Since the passage of the revised FDCA in 1938, a lengthy, complex process for safety-testing new drugs has evolved, along with a requirement that new drugs be safe and effective. The idea for a drug product is first researched in the laboratory. If the substance shows promise, tests are performed in animals to determine how the drug is handled in the body and whether the substance appears safe for human testing. In 1975, FDA inspections of animal testing laboratories revealed poorly conceived and carelessly executed experiments and badly run animal facilities. These deficiencies led the FDA to institute the Good Laboratory Practice regulations to control studies of drugs in animals.

If a drug appears safe and efficacious in animal studies, investigators prepare a plan to investigate the product in human volunteers. They submit their plan to the FDA Investigational New Drug Application (IND). If FDA reviewers decide the IND is acceptable, the company can move into human testing.

Good Clinical Practices are regulations that govern trials of drug safety and efficacy in humans. Clinical trials are conducted in stages. Phase I trials are the first introduction of the proposed drug into humans, whereby the safety of the drug is evaluated in healthy volunteers. If a drug meets the safety requirements at this phase, then it enters Phase II trials involving a small number of diseased patients. If the drug meets safety requirements and demonstrates efficacy at Phase II, it progresses to a broader Phase III clinical trial.

If a drug passes all three phases of testing, the company may submit an application, called a New Drug Application (NDA), to the FDA documenting their evidence that the drug is safe and effective. If the
FDA reviewers decide the evidence is sufficiently favorable, the new product is approved and can be manufactured for sale.

THE BEGINNING OF THE THALIDOMIDE STORY

Thalidomide was first synthesized in 1953 by a West German company (McFadyen 1976; Hoffmann 1997). Early tests in animals and humans indicated that the drug had little toxicity and that in humans it promoted sleep, although it did not have any sedative effect on animals. By 1957 the drug was introduced to the West German market and soon became a popular sleeping pill, taken by both adults and children. Thalidomide could be ingested in large quantities without apparent harm and was thought to be so safe that it did not require a prescription. Moreover, the drug prevented nausea due to pregnancy and was frequently used for this purpose.

Eventually the German manufacturer began to license the distribution of thalidomide in other countries. The American pharmaceutical firm, William S. Merrell Company, wanted to distribute thalidomide in the lucrative U.S. market. On September 12, 1960 the FDA received an NDA from Merrell requesting approval for thalidomide. The NDA contained glowing claims for the drug and reports of animal and human tests indicating the drug’s therapeutic dosage and its presumed safety. Since thalidomide was already widely used, the NDA was thought to be routine and was assigned to the agency’s newest medical officer, Dr. Frances Oldham Kelsey. Kelsey later explained that "They gave it [the NDA for thalidomide] to me because they thought it would be an easy one to start on. As it turned out, it wasn't all that easy". (Burkholz 1997)

Frances Kelsey was born in Canada and later became a naturalized American citizen. She attained a Ph.D. degree in pharmacology at the University of Chicago where, as a graduate student, she played a small role in the investigations to determine why Massengill’s sulfanilamide elixir was harmful. Dr. E.M.K. Geiling and his colleagues at the University of Chicago performed pharmacologic and pathologic studies of animals treated with the Massengill product. It was these animal studies that revealed that diethylene glycol was the drug’s toxic component. As Kelsey later reported, “All graduate students were required to watch the progress of all these studies and to lend their assistance, wherever possible...”(Kelsey 1993). In a speech prepared for the Medical Alumni Association of the University of Chicago, Kelsey said: “The urgency of the situation, the intensive round-the-clock toxicological studies and the subsequent changes in the law relative to the control of drugs could not and did not fail to make a deep impression on a graduate student such as myself in the University’s Department of Pharmacology.” (Kelsey 1963)

In 1950 Dr. Kelsey completed her medical degree and after graduation worked as an editorial associate for the American Medical Association (AMA) Journal. As she reported, “I soon learned...that good scientists are almost invariably good writers and that poor writing is often a sign of poor science ... when I came to the Food and Drug Administration..., I found that many of the studies in support of safety of the new drugs were done by investigators whose work had not been accepted for publication in the Journal [of the AMA]” (Kelsey 1993).

In 1952, Dr. Kelsey and her family moved to South Dakota where she taught pharmacology and worked as a temporary doctor in small communities. In 1960 she was hired by the FDA to review applications for drug approval.
QUESTIONS

1a. Outline the steps that the Merrell Company needed to go through to have thalidomide approved in the U.S.

b. If you were Dr. Kelsey, what sort of scientific studies would you be looking for in the thalidomide NDA?

2. Thalidomide had been tested previously in West Germany and, compared to other sedatives, was safe at high doses. It was widely used in Europe with apparently few, if any, problems. The Merrell company was anxious to have the drug marketed. If you were Dr. Kelsey, would you approve the drug for distribution in the U.S.?

Stop. Do not read further until the class has discussed these questions.
Dr. Kelsey reviewed the NDA from Merrell Company in collaboration with an FDA chemist and a pharmacologist. The pharmacologist and chemist both noted omissions in the NDA. For example, the chronic toxicity data were incomplete, meaning that no evaluation could be made of the safety of the drug when used for prolonged periods of time. The chemist found numerous deficiencies relating to details of the manufacturing processes and the methods used to determine the identity, strength, and purity of the new drug substance. The reviewers were concerned that thalidomide did not put animals to sleep because this suggested that there are differences in the way humans and animals absorb or metabolize the drug (Kelsey 1963). Such differences made the animal safety studies suspect.

According to the laws at that time, Merrell would have been able to market thalidomide if the company had not heard back from the FDA within 60 days of submitting their NDA. Therefore, if Dr. Kelsey had done nothing at this point the drug would have been marketed. Indeed, Merrell was poised to begin distribution in the U.S., having brought in at least 5 tons of thalidomide to its warehouses (McFadyen 1976). Instead, on November 10, Dr. Kelsey sent a letter to Merrell outlining the deficiencies noted by the reviewers and asking for more testing.

The Merrell company was anxious to get the drug approved and began a campaign to push the application through the FDA approval process. Dr. Joseph Murray of the Merrell Company repeatedly called and visited FDA. However, Dr. Kelsey resisted approving the drug because of concerns about the adequacy of the safety data in the NDA.

Five months after the NDA was submitted, Dr. Kelsey learned about the occurrence of peripheral neuritis (deterioration of the nerves in the hands and feet) in patients who had used thalidomide over a long term. Merrell Company investigators reported that the incidence of peripheral neuritis was low and the condition was rapidly reversible. Merrell suggested that a caution about this side effect be put onto the drug label and that it then be approved. However, by this time Kelsey and other reviewers were even more concerned about the drug and refused to approve it.

While this concern about peripheral neuritis was simmering, FDA reviewers voiced another issue. Thalidomide was used by pregnant women and the reviewers considered the possibility that a fetus might be harmed by the drug. Kelsey had been involved in studies of the antimalarial drug, quinine, performed at the University of Chicago. She knew that a rabbit fetus lacked the ability to metabolize quinine; the required enzyme appeared only after birth. Subsequent studies showed that many drug-metabolizing enzymes are absent in the fetus. As Kelsey (1993) later explained "... at this time there was growing concern regarding the exposure of the fetus to drugs and other substances to which the mother was exposed during pregnancy." Dr. Kelsey brought up her concerns regarding possible harm to a fetus to Dr. Murray. Merrell responded by showing studies indicating that the drug was safe in the third trimester of pregnancy, but FDA asked for evidence that it was safe throughout gestation. Merrell then suggested releasing the drug with a warning on the label that the safety of the drug during pregnancy was not established, but Kelsey did not accept this suggestion (Kelsey 1993).

The pressure on Dr. Kelsey and the FDA intensified during the spring and summer of 1961. "They came to Washington, it seemed, in droves. They wrote letters and they telephoned - as often as three times a week. They telephoned my superiors and they came to see them too...Most of the things they called me, you wouldn’t print", recalled Dr. Kelsey (Mulliken 1962). Despite the intense pressure, Dr. Kelsey continued to ask for more proof of the drug’s safety.
QUESTIONS

3. If you were an FDA reviewer, what would you have done at this point?

4. Dr. Kelsey was under tremendous pressure to approve thalidomide. Why do you suppose she resisted the pressure?

Stop. Do not read further until the class has discussed these questions.
THE STORY CONTINUES

In late November, 1961, more than a year after the drug application was submitted to FDA, Dr. Murray called Dr. Kelsey and told her that thalidomide was being withdrawn from the German market because of reports of congenital abnormalities in children born to mothers who had used it. By 1962 it was clear that the drug caused crippling malformations of the arms and legs. Children had been born with hands and feet protruding directly from their torsos. Others had limbless trunks with toes extending from their hips; others were born with just a head and a torso; still others had cardiac problems. It is estimated that anywhere from 8,000 to 80,000 thalidomide-deformed babies were born in Europe. Because of the stubborn skepticism of Dr. Kelsey and others in the FDA, this tragedy was largely averted in the U.S. For her efforts, Kelsey received the President's Distinguished Federal Civilian Service Award in 1962, the highest civilian honor available to government employees.

INVESTIGATION

During the time the NDA was being reviewed, Merrell had distributed thalidomide to more than 1000 physicians, supposedly for “investigational use.” This distribution of a drug for research purposes was not illegal at that time, although FDA had thought only 35-60 physicians were “investigating” the drug.

On July 20, 1962 the executive vice president of Merrell told the FDA commissioner that a recall of thalidomide distributed to U.S. doctors was complete. However, an FDA inspector visiting the Merrell offices found employees still in the process of contacting the many physicians who were thought to have received the drug. The FDA subsequently discovered that many doctors who had distributed thalidomide had made no effort to contact patients to whom they had given it and, indeed, often had no records of those whom they had given the pills. An FDA survey showed that more than 2,500,000 tablets had been distributed to over 20,000 patients. Eventually 10 well-documented cases were found in the U.S. of women who had received thalidomide during pregnancy and delivered seriously deformed babies (McFadyen 1976).

There was ample evidence that the Merrell company’s distribution of thalidomide supposedly for research purposes was, in fact, part of a marketing campaign. It was eventually decided, however, that there was not sufficient evidence to prove that they had withheld knowledge of the drug’s adverse effects. The justice department declined to press criminal charges against Merrell although there were at least ten civil lawsuits against Merrell that resulted in settlements to families with disabled children.

POLITICS

Dr. Helen Taussig, a physician, visited Europe shortly after the effects of thalidomide were discovered. When Taussig returned to the U.S. she wrote articles and speeches reporting on the effects of thalidomide in Europe and the narrowly averted tragedy in the U.S. Despite her efforts to bring this story to the attention of the American people, she received little press. Meanwhile, Senator Estes Kefauver of Tennessee had been involved for several years in an in-depth investigation of the drug
industry. He was primarily interested in reducing drug prices, but he also had unsuccessfully introduced a bill to tighten drug safety regulations. In the summer of 1962, one of Kefauver’s staff read about Dr. Taussig’s speeches. Senator Kefauver and his staff decided to promote the story to help the passage of their proposed legislation. Kefauver convinced a reporter from the prestigious Washington Post newspaper to interview Dr. Kelsey. The Washington Post printed the story on page one and it was followed by a media blitz with numerous follow-up stories around the country.

As had occurred in response to the sulfanilamide tragedy, the thalidomide incident mobilized public demands for stronger drug regulations. Senator Kefauver’s previously unsuccessful bill was resurrected and passed in 1962 as the Kefauver-Harris Drug Amendments to the FDCA. These amendments strengthened the regulation of drugs and tightened the rules governing the conduct of drug testing in humans so that physicians could not casually distribute investigational drugs (as had occurred with thalidomide).

**QUESTIONS**

5. What records would a company need to maintain in order to be able to effectively recall a drug that had been widely distributed? What would it be like to work in a company maintaining these records?

6. a. What is the role of Congress in ensuring drug safety?
   b. What is the role of the FDA in ensuring drug safety?
      c. What is the role of a pharmaceutical company in ensuring drug safety?
   d. What is the role of the consumer in ensuring drug safety?

7. Suppose you are hired as a representative of the pharmaceutical industry. Prepare a position paper for the industry on regulation. What principles would you advocate? What would be your position on government regulation of your industry? Prepare arguments to support your position.

8. AIDS patients have expressed frustration at the slow rate at which drugs are developed to treat their illness. Drug companies attribute the slowness to stringent drug testing requirements. Patients argue that they are dying while safety studies are conducted. Therefore, FDA has provided avenues by which AIDS patients can obtain drugs that have not been fully tested. What do you think about this “fast-tracking” of AIDS drugs? What do you think of allowing patients with less serious conditions access to drugs that are not well-tested and might pose unknown risks?

9. Currently, herbal preparations (such as Saint John’s Wort that is popularly used for depression) are not required to meet the requirements enforced by FDA. Therefore, there is limited oversight to ensure that herbal preparations have been tested for safety, or that they are processed properly. Some people think that herbal preparations should be FDA-regulated to protect consumers. Others fear that government oversight of these products will cause them to become more expensive and less available. What do you think?

10. How do public opinion and politics influence drug regulation?
POSTSCRIPT

Thalidomide is now known to have complex, multiple effects on the body. One effect is that it inhibits new blood vessel growth (angiogenesis). This is detrimental to a fetus because angiogenesis provides a "road map" for the growth of limbs and organs during development. The way that thalidomide acts in the body is still being deciphered. You can read about it at: http://www.nytimes.com/2010/03/16/science/16limb.html.

Interestingly, it has been found that thalidomide, despite its terrible effects on a developing fetus, may be useful in treating some diseases. For example, thalidomide is being investigated as a treatment for breast, prostate, and brain cancer by inhibiting angiogenesis.

In the 1960s, an Israeli physician gave thalidomide to leprosy patients to help them sleep in spite of painful, disfiguring lesions caused by their disease. Surprisingly, thalidomide not only sedated the patients, it also helped to heal the lesions (Kling 2000).

In 1998, FDA approved thalidomide for the treatment of leprosy and in 2006 for treatment of multiple myeloma. The dispensing of the drug is tightly controlled in an effort to keep it from being used by pregnant women.

QUESTION

10. What do you think about the use of this drug for treating varied disorders? Is it acceptable to distribute a drug that is known to cause severe birth defects, since once a drug is distributed it might find its way into pregnant women?

REFERENCES

Food and Drug Administration. The FDA homepage is http://www.fda.gov. The information on this website changes frequently. Search for thalidomide for the most current articles.


Kelsey, F.O. (December 9,1993). Denial of Approval for Thalidomide in the United States. Speech presented at the National Library of Medicine, Bethesda, MD.


