Debunking the Mystery of Accutane

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The cliché answer to why history is important is, so that we do not repeat the same mistakes we made in the past. However, often, before we even realize it, we end up going down the same road that leads to unfavorable consequences. Why does this happen? Perhaps some people do not view a set of outcomes as a "mistake," and thus, choose to pursue the same path. Or perhaps the road was cut short in the past, and the second time around, people want to make sure that they see the end of the road and fulfill their agenda. Or perhaps no one made sense of the events early enough to prevent a repeat from happening again. It is quite a mystery why we allow for a series of unfortunate health events to occur again, particularly, if a set of events seem significant and recent enough to remain in the minds of the involved parties and the public. In the history of the U.S. pharmaceutical industry, such a mystery has yet to debunked.

In the 1960s, thalidomide, a potent drug to treat sleeplessness, became known to the U.S. public, following its release on European markets in the late 1950s. The manufacturer Richardson-Merrell Inc. had distributed 2.5 million thalidomide pills for testing purposes in the U.S., but the drug was never sold nor approved to be sold there.[1] However, before the FDA was able to approve thalidomide for sale on U.S. markets, evidence linking the births of deformed children to their mothers taking the drug early in pregnancy became available. These cases along with other scientific findings raised red flags for FDA medical officer, Dr. Frances Kelsey, who successfully stopped thalidomide from reaching U.S. markets. However, in 1981, when an application for a highly effective acne-treating drug, known as Accutane (generically called "isotretinoin"), was submitted to the FDA to be marketed in the U.S., it was quickly approved in the following year, with a pregnancy category X, due to clear evidence of the drug's ability to cause malformations in babies whose mothers had taken Accutane. According to the Office on

[1] Morton Mintz, "She's 19, Deformed, And Family Is Suing Thalidomide Maker," *Washington Post,* November 15, 1980, accessed October 12, 2016.

Women's Health, a pregnancy category of X means, "Studies or reports in humans or animals show that mothers using the medicine during pregnancy may have babies with problems related to the medicine. There are no situations where the medicine can help the mother or baby enough to make the risk of problems worth it. These medicines should never be used by pregnant women."[2] Given that the thalidomide incident occurred only about 20 years prior, one would think that the FDA would not only reject Accutane's application, but also impose stricter restrictions on which drugs could be placed on the market and how they should be advertised. However, Accutane's application was classified as top priority, and the drug was very quickly approved, which was viewed with surprise by many. Was the quick approval of a drug that was clearly linked to the births of children with physical deformities Accutane's only "odd" point of interest? Did any medical experts notice the similarity in side effects between thalidomide and Accutane, and fear the consequences of approving Accutane for U.S. markets? Given that the thalidomide tragedy was heavily covered by the media, did Accutane also receive as much attention from the media? It turns out that while there had been substantial media coverage on both the thalidomide and Accutane incidents during the time, modern historians have primarily only written about thalidomide.

Personally, the Accutane case presents itself as a greater mystery than the thalidomide case does – Accutane came *after* the thalidomide incident, clear evidence of Accutane's ability to cause physical deformations in babies was available earlier in the approval process than for thalidomide, and the international community was sending warnings to the U.S. and imposing very strict restrictions on Accutane use and administration in their respective countries – yet,

[2] "Pregnancy and medicines fact sheet," Office on Women's Health at the U.S. Department of Health and Human Services, last modified July 16, 2012, accessed December 10, 2016, https://www.womenshealth.gov/publications/our-publications/fact-sheet/pregnancy-medicines.html.

despite all of these events which I expect would have contributed to devising potential efforts to significantly reduce the number of births of deformed children, the FDA proceeded to approve Accutane for sale on U.S. markets. Thus, given the lack of historical analysis done on the mysterious case of Accutane, this paper will analyze newspaper articles, other primary sources, and secondary sources, in an attempt to construct and retell the story of Accutane. It will consider the important actors, visible and invisible; question the effectiveness of FDA regulations; and synthesize the journalists' opinions on the expected role of the FDA in protecting the consumers. This paper will argue that the news articles written at the time did not contain the full narrative, which contributed to the mysterious nature of the Accutane incident. However, once the holes in the narrative were filled, other primary sources and case studies could address the reasons for the lack of effective FDA regulations in controlling the use of Accutane.

Thalidomide – the story

A deeper look at thalidomide further reveals why the Accutane incident is a mysterious case. Thalidomide was considered a "miracle" drug that was the safest and most effective sedative that had ever been developed. In fact, in West Germany, the drug was considered so safe that it could be sold without prescription.[3] In 1958, thalidomide went on the market in many European countries, and a year later, "a dozen grossly deformed infants were born."[4,5] Phocomelia, or malformed fingers or toes that looked like flippers, was the resulting condition. Questions such as, "Wasn't the placenta a marvelous protection for the fetus? Didn't it prevent

[3] William Grigg, "The Thalidomide Tragedy – 25 Years Ago," *FDA Consumer,* February 1987, accessed October 12, 2016.
[4] Ibid.
[5] See Figure 1. Judith Willis, "New Warning About Accutane and Birth Defects," *FDA Consumer,* October 1988, accessed October 12, 2016.

harmful substances in a mother's blood from reaching the unborn child?" were raised.[6] Through the thalidomide controversy, such popular misconceptions were addressed. In 1960, the William S. Merrell Co. of Cincinnati submitted an application for thalidomide to the FDA. However, due to the persistent efforts of FDA medical officer Dr. Frances Kelsey, who wanted to be certain that thalidomide was safe before she approved its marketing application, the William S. Merrell Co. withdrew its application when numerous reports proved the linkage between thalidomide and phocomelia, and when other countries were taking the drug off their markets. Dr. Helen Taussig, professor of pediatrics at Johns Hopkins University, said to fellow physicians at the annual American College of Physicians, "This compound [thalidomide] could have passed our present drug laws. There is no question we need to strengthen our food and drug regulations to include routine testing of new compounds on pregnant animals."[7] In fact, the thalidomide incident did lead to some major changes in drug regulations.

Thalidomide is also an example of how the U.S. was "attentive" to the responses of other countries and consequently, initiated its own reform quite successfully. ("Attentive" meaning not only aware of and paying attention to, but also taking measures similar to those of other countries and/or following their lead, in order to prevent future disastrous consequences from happening in the U.S.). John Abraham, a sociologist at the University of Reading in England, explains in his book, *Science, Politics and the Pharmaceutical Industry,* that compared to in the U.K., the number of affected children in the U.S. was much smaller, as a result of Frances Kelsey's efforts to delay the approval of thalidomide.[8] Furthermore, of the estimated 7,0000 to 11,000 thalidomide babies born worldwide, about 1,200 of those babies were born in Japan and

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[6] Grigg, "The Thalidomide Tragedy."
[7] Ibid.
[8] John Abraham, *Science, Politics and the Pharmaceutical Industry: Controversy and bias in drug regulation* (New York: St. Martin's Press, 1995), 62.

just 17 were born in the U.S..[9,10] Nevertheless, there was immense support for drug regulation reform in both European countries and the U.S., especially given that by this time, European physicians had discovered a causal relationship between the drug taken during pregnancy and phocomelia.[11] Particularly in the U.K., there was an increased focus on improving drug *safety* evaluations.[12] However, in the U.S., the thalidomide incident mainly led to reforms related to drug *efficacy*, since "the U.S. already had substantial safety regulations in place."[13] Except for the Oren Harris' House Bill, which gave the FDA the power to withdraw immediately from the market a drug which posed an "imminent hazard to public health," all other new laws focused on drug efficacy.[14] For example, the Kefauver bill required that drugs were presented with "substantial evidence" of efficacy, which meant that there should be "adequate and well-controlled investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved." (The Oren Harris' House bill and the Kefauver bill were signed into the 1938 Food, Drug, and Cosmetic Act as the Kefauver-Harris Amendment in October 1962). In *Reputation and Power,* author Daniel Carpenter quotes Philip Hilts who explained that "after the Kefauver hearings, thalidomide and the new law [Kefauver-House Act], the FDA was now seen as a potential serious force, one that could protect the public in an emergency."[15] However, although new regulations and policies did elevate the FDA's sense of

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[9] Kaoruko Aita, "The bad blood legacy," *Japan Times,* April 8, 1996, accessed December 9, 2016, http://search.proquest.com.ezp-prod1.hul.harvard.edu/docview/218954754?rfr_id=info%3Axri%2Fsid%3Aprimo.
[10] Sheryl Gay Stolberg, "37 YEARS LATER, A SECOND CHANCE FOR THALIDOMIDE," *New York Times,* September 23, 1997, accessed December 9, 2016, http://search.proquest.com.ezp-prod1.hul.harvard.edu/docview/109793449?rfr_id=info%3Axri%2Fsid%3Aprimo.
[11] Abraham, *Science,* 62.
[12] Ibid.
[13] Abraham, *Science,* 63.
[14] Ibid.
[15] Daniel Carpenter, *Reputation and Power* (Princeton: Princeton University Press, 2014), 120.

power and role in the pharmaceutical industry, as we will see later on through the case of Accutane, its power was clearly not strong enough – or rather, perhaps the fundamental problem was never even about how much power the FDA had. It is possible that the FDA already had the necessary power and abilities, but either involuntarily or voluntarily, decided not to fully execute its power. In fact, according to the newspaper articles written at the time, even with the thalidomide story, the reason for the relatively happy ending in the U.S. is the story's heroine, Dr. Frances Kelsey; the story told by the media barely even included any details on how the FDA's power was severely limited and so restricted it could not take certain actions…

Merely based on primary source analysis of newspaper articles written during the thalidomide controversy, it would appear that Dr. Frances Kelsey and her persistence were the sole reason thalidomide did not hit the U.S. as badly as it hit Europe. However, what the journalists do not tell is the political efforts that were taking place in the background to gather support for stricter drug regulations. Primary sources have revealed how journalists portrayed Dr. Frances Kelsey, a medical officer working at the FDA, as the 'heroine' in the thalidomide story – the title of one of journalist Morton Mintz's articles was "'Heroine' of FDA Keeps Bad Drug Off of Market."[16] Mintz wrote that given the inconsistences between the drug's effects in humans and in animals, and evidence of malformed births in experiments on animals, Dr. Kelsey could not help but regard thalidomide as a "peculiar drug."[17] Thus, she was persistent in delaying the approval of the drug, especially since thalidomide "was not, after all, intended for grave diseases, or for the relief of intolerable suffering, but primarily for sleeplessness, for which many drugs of known safety were already on the market."[18] Therefore, Dr. Kelsey's role was crucial in reducing

[16] Morton Mintz, "'Heroine' of FDA Keeps Bad Drug Off of Market," *Washington Post,* July 15, 1962, accessed September 20, 2016.
[17] Mintz, "'Heroine' of FDA."
[18] Ibid.

the impact of thalidomide's harmful health effects in the U.S. In fact, Harvard professor Daniel Carpenter claims that this article was "the decisive event linking thalidomide and the FDA" and states Mintz's point as "were it not for Kelsey's resistance to the Merrell overtures thousands of American families may well have experienced the fate of thalidomide victims in Europe and Australia and other countries."[19] However, what Carpenter points out about Mintz's article that is not obvious from the article, but a crucial feature is the story's author: Tennessee Senator Estes Kefauver's antitrust subcommittee.[20] The subcommittee leaked the details, and some data and documentation to Mintz, who then contacted Dr. Kelsey. Thus, according to Carpenter, "Frances Kelsey's public triumph was not a newspaper scoop… but instead a carefully timed leak designed to influence the passage of impending legislation, in this case Kefauver's drug regulation bill (S.1552)."[21] Following Mintz's article, publicity about thalidomide and about Dr. Kelsey grew, and the public's image of the FDA was that "if given the discretion and the resources, FDA medical officers [would] make the right decision, most of the time."[22] Thus, though indeed Dr. Frances Kelsey was a key player whose stubbornness and resistance throughout the drug approval process significantly contributed to preventing thalidomide from reaching U.S. markets, she was not the sole actor and her portrayal as a 'heroine' was actually a carefully orchestrated attempt by Congress and its committees to boost the FDA's national reputation, which would help pave the way to new regulation, such as the Kefauver-Harris Amendment.

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[19] Carpenter, *Reputation*, 242.
[20] Ibid.
[21] Ibid.
[22] Carpenter, *Reputation,* 251.

Accutane – the mystery

Given that all of these crucial factors, though some more than others, played a role in thalidomide's regulatory success, there are key differences between the thalidomide case and the Accutane case that may explain why Accutane was approved and why it was on the market for so long, despite the recent history of the thalidomide incident.

Like thalidomide, Accutane was known as a "wonder drug;" it was the only available drug potent enough to cure mutilating acne. According to a special report by the *New York Times,* Accutane has "extraordinarily beneficial effects on skin tissue by combatting virtually all the mechanisms that create acne… [and] many regain completely clear skin."[23] Yet, Accutane was classified as pregnancy category X. Within about a year since Hoffman-La Roche Inc.'s marketing application for Accutane was approved by the FDA, the first reports of abortions and birth defects became available. Of the 150 young women who became pregnant while exposed to the drug, about 100 had elective or spontaneous abortions and 28 had infants with birth defects.[24] What is important to note is that numerous newspaper articles that covered the Accutane case included the detail that by the time the drug was placed on the market in September 1982, there was already a lot of evidence that Accutane caused birth defects. Yet the FDA and Hoffman-La Roche Inc. neither decided to conduct further studies before approving the drug nor took any precautionary safety measures when they marketed it. It was only after the first report of birth defects came out that Hoffman-La Roche Inc. "recommended that a pregnancy test be given prior to starting the drug."[25] Given the two important facts, first, that clear evidence of birth defects was available to Hoffman-La Roche Inc. and the FDA at an earlier stage than it was to

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[23] Sandra Blakeslee, "Drug That Often Cures Acne Can Also Cause Birth Defects," *New York Times,* October 29, 1984, accessed October 30, 2016.
[24] Blakeslee, "Drug That Often Cures."
[25] Ibid.

William S. Merrell Co. and the FDA at the time, and second, that chronologically-speaking, Accutane came twenty years after thalidomide, the case of Accutane seems quite mysterious. Why did Accutane make it onto the markets without any major restrictions to its prescription and use? Though the full (and even completely true) story is most likely not revealed through the media, through close analysis of newspaper articles published during the Accutane controversy, part of the mystery can be pieced together.

First, it is important to identify the major contrasting features between the thalidomide tragedy and the Accutane case because they contribute to explaining why the Accutane story had a very unexpected plotline. These differences include the lack of transparency of Hoffman-La Roche's research on and development of Accutane, the lack of an individual like Dr. Frances Kelsey, the lack of a strategic "leak" of information in attempt to garner public support, the lack of "attentiveness" to how other countries were addressing the incident, and the lack of prompt regulation reforms that were as new and effective as the ones that the thalidomide case led to. Citing *Hoffmann-La Roche v. Yoder, 950 F. Supp. 1348 (Ohio 1997)* and *Hammock v. Hoffmann-La Roche, 622 A.2d 546 (N.J. 1996),* Julia Green summarizes that the Hoffman-La Roche company repeatedly went to court and demanded that any information regarding the development of Accutane be kept private.[26] In addition, the company was intentionally vague about the wording of their labels. The FDA turned to the Dermatologic Drugs Advisory Committee for advice when it received Hoffmann-La Roche's application for FDA approval in July 1981.[27] In January 1982, the Committee provided two suggestions to the FDA: one, that

[26] Julia Green, "Babies, Blemishes and FDA: A History of Accutane Regulation in the United States (2002 Third Year Paper)," 5, accessed October 30, 2016, https://dash.harvard.edu/bitstream/handle/1/8963867/Green.pdf?sequence=1.
[27] Green, "Babies, Blemishes," 6.

they approve Accutane, and two, that the label be changed.[28] Regarding the second suggestion, while in the animal studies, Hoffmann-La Roche researchers discovered that the subjects' offspring had facial deformities, they completely excluded pregnant women in their clinical trials. Thus, when Hoffmann-La Roche proposed a pregnancy risk rating of C, in its application for approval, the FDA decided to classify the drug as category X, which meant that the risk to the fetus outweighed any potential benefit to the pregnant woman.[29] However, the label still did not specify that there had been no evidence of birth defects in humans precisely because pregnant women were excluded in the clinical trials.[30] Then, in May 1982, the FDA approved Accutane, and the drug was classified as "1A," top priority; according to a Hoffman-La Roche spokeswoman, "approval came through so fast that it came as quite a surprise to everyone…"[31] As seen in the case of thalidomide, the presence of a persistent individual like Dr. Frances Kelsey and a particular political agenda were crucial to the successful prevention of the drug's approval; however, other important factors included the coordination, timing, and circumstances that were present at that given time and not present during the Accutane incident. Thus, give that Accutane was surprisingly approved very quickly, how favorably the drug's treatment effects were spoken of in the early stages of development, and the extremely high numbers of prescriptions within the first six months of marketing, it is likely that the FDA, Hoffmann-La Roche, or both, were eager to put Accutane out on the markets. In order to better understand the roles of the FDA and Accutane's manufacturer in the controversy, we must first identify the powers the FDA had at the time.

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[28] Green, "Babies, Blemishes," 7.
[29] "Testimony of Dr. Colonel Evans before the Dermatologic Drugs Advisory Committee," 37, May 8, 1989, accessed October 30, 2016, http://www.fda.gov/ohrms/dockets/ac/accutane/29t1.pdf.
[30] Green, "Babies, Blemishes," 7.
[31] Penny Chorlton, "FDA Outpaced Firm on Acne Drug," *Washington Post,* September 14, 1982, accessed October 30, 2016.

The complexity of U.S. drug regulation is evident in the Accutane case. Since the drug had already been approved for marketing, the FDA had no legal authority to restrict doctors' rights or reinforce tighter regulations. Thus, given that the Kefauver-Harris Amendment was passed in 1962, many years before Accutane's release, it is puzzling as to how Hoffmann-La Roche's application for Accutane was approved given the drug's questionable safety.

According to the Congressional Research Service Report for Congress, in order to prove drug safety and effectiveness, the U.S. Federal Food, Drug, and Cosmetic Act (FFDCA) requires "substantial evidence," which means, "at least two adequate and well-controlled Phase III clinical studies, each providing convincing evidence of effectiveness."[32] However, Susan Thaul, the author of the report, states that the FDA's definition and standards for what is "evidence" is flexible.[33] The FDA then reviews the application and evaluates the "clinical and nonclinical research evidence of safety and effectiveness, manufacturing controls and facility inspection, and labeling."[34] In terms of postmarket regulatory procedures (at this point, the drug is "FDA-approved"), manufacturers must report "all serious and unexpected adverse reactions" to the FDA; postmarket drug safety and effectiveness activities have traditionally involved these nine activities: product integrity, labeling, reporting, surveillance, drug studies, risk management, information dissemination, off-label use, and direct-to-consumer advertising.[35] What is very interesting to note in this CRS Report is that it states, "Researchers debate the effectiveness of labeling," and cites a study of physician compliance that concludes that doctors violated black-

[32] Susan Thaul, "How FDA Approves Drugs and Regulates Their Safety and Effectiveness," *Congressional Research Service Report for Congress,* June 25, 2012, accessed December 10, 2016, https://fas.org/sgp/crs/misc/R41983.pdf.
[33] Thaul, "How FDA Approves," 5.
[34] Thaul, "How FDA Approves," 6.
[35] Thaul, "How FDA Approves," 8-9.

box warnings in 7% of prescriptions.[36,37] The topic of labeling and its effectiveness is important to consider in the Accutane case because much of the regulation of the drug occurred at the level of labeling. Thus, this paper will revisit this topic in a later section and analyze the effectiveness of labels in warning patients about health risks and harms, in the contexts of tobacco and Accutane.

Regulating Accutane

Major changes and responses to Accutane began to occur in 1988, six years after the drug was marketed in the U.S. From Gina Kolata's piece in the New York Times, "Europeans Placed Stiffer Curbs on Acne Drug," and Lawrence Altman's article, "U.S. Orders Curbs on Drug Linked to Birth Defects," it is evident that many felt like the FDA's restrictions were not strict enough.[38, 39] Kolata supported her claims by comparing what was being done in the U.S. to that in European countries. According to her sources, restrictions in the U.S. to control the use of Accutane had not been very strict. While in the U.S., the drug was only accompanied with a caution label, in other countries, usage was more strictly limited to essential cases and non-pregnant women. Kolata stated that despite U.S. officials having been aware of what other countries were doing, and despite the concerns expressed by European doctors about the U.S.' lax control, it was not until April 1988, when the FDA and CDC estimated hundreds of babies would be severely deformed, that an actual move towards policy change took place in the U.S.[40]

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[36] Thaul, "How FDA Approves," 11.
[37] Karen E. Lasser, Diane L. Seger, D. Tony Yu, et al., "Adherence to Black Box Warnings for Prescription Medications in Outpatients," *Archives of Internal Medicine* 166 (February 13, 2006): 338-344.
[38] Gina Kolata, "Europeans Placed Stiffer Curbs on Acne Drug," *New York Times,* April 28, 1988, accessed October 12, 2016.
[39] Lawrence Altman, "U.S. Orders Curbs on Drug Linked to Birth Defects," *New York Times,* May 27, 1988, accessed October 12, 2016.
[40] Kolata, "Europeans Placed Stiffer Curbs."

At an advisory board meeting, a few days prior to April 28, 1988, new estimates from Medicaid programs in Michigan and Florida, and from a health maintenance organization in Washington state, were given: of the 9180 American women who took the drug while pregnant, 597 of their babies were born with severe birth defects from 1982-1986.[41] Although Kolata's tone was neutral, through her references and presentation of facts, she hinted that she, along with many American and European experts, were concerned with how the U.S. was not adequately dealing with Accutane. Despite warnings from multiple sources, such as, scientific evidence from experiments on laboratory animals and extreme measures other countries were taking, it took six years for the FDA to take some sort of action to address the severity of Accutane's effects. Kolata revealed a bit of her puzzlement and concern regarding the fact that though experimental results on laboratory animals revealed Accutane's causing of birth defects *before* the drug was even approved, and given the prior history of thalidomide, Accutane was still marketed. She wrote, "In the case of thalidomide in the 1960's, the drug… was not permitted in the United States by officials who saw cause to worry. But with Accutane, which has been compared in severity to thalidomide, it was the United States that first approved marketing and imposed less restrictive distribution than many other countries who later approved the drug."[42] She contrasted the U.S.' behavior to England and Spain's by noting that Accutane and thalidomide were regulated in the same way in England and Spain: the uses of the two drugs were strictly limited among women.[43] In fact, she explicitly stated that Accutane was an example that "runs counter to an image commonly drawn by critics of the FDA who say its overly cautious policies deny Americans access to important drugs available abroad."[44] In this way, she questions how strict

[41] Ibid.
[42] Ibid.
[43] Kolata, "Europeans Placed Stiffer Curbs."
[44] Ibid.

the FDA's restrictions are in reality, and criticizes the delayed and lax restrictions implemented by the FDA. Thus, by comparing the U.S.' response to Accutane to its response to thalidomide, Kolata demonstrates the puzzling nature of the lax restrictions on Accutane use, the lack of urgency to regulate Accutane, the unexpected approval of the drug (given that evidence of its teratogenic effect was available earlier in the process compared to thalidomide), and the stark contrast between the U.S.' response and Europe's response.

Regarding the new restrictions that the FDA decided to implement a few days before Kolata wrote her piece, Kolata's tone remained skeptical and not too impressed. She contrasted the FDA advisory board's new requirement of second medical opinions before the administering of prescriptions, with European countries' strict restrictions: for example, in Britain, Accutane and thalidomide are in a special group of drugs, which only 350 selected dermatologists are allowed to prescribe; and in Sweden, Accutane is not on the market, but doctors can make special requests to the government and justify their patients' needs for the drug.[45] Kolata discussed many more examples in other countries, but already from these two examples, it is evident that she viewed the FDA restrictions to be very lax in comparison to other countries'. As an explanation for this notable difference, Kolata suggested that given that thalidomide was never approved for marketing in the U.S., Europe was hit much harder by thalidomide than the U.S., and as a result, European countries were imposing much stricter restrictions on Accutane prescriptions. In her article, Kolata quoted a doctor, who expressed this very logic, "Accutane is as bad as thalidomide, but it doesn't have the emotional connotation of thalidomide. As a group of doctors who lived through thalidomide, we are much more careful about using Accutane."[46]

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[45] Ibid.
[46] Kolata, "Europeans Placed Stiffer Curbs."

Thus, journalists and doctors alike sensed both an emotional response and an urgency to severely restrict the use of Accutane.

About a month later after Kolata's piece appeared in the New York Times, Lawrence Altman also wrote an article in the New York Times about restrictions that were implemented by the FDA, shortly after Accutane was marketed. On May 19, 1988, the FDA wrote a letter to Hoffmann-La Roche Inc. ordering the manufacturer to take stronger measures to prevent use by pregnant women, such as including a photograph of a deformed child in the warning label of the product, requiring patients to sign a consent form indicating that they are aware of the risks and are taking measures to prevent pregnancy.[47] Other restrictions included statistics on the warning label ("at least one chance in four that Accutane use in pregnancy will result in a deformed infant"), and filling of prescriptions only after a new menstrual period began to ensure that the women were not pregnant.[48] However, some government health officials and private experts did not think that these restrictions were strong enough; instead, they wished that there were a total ban or measures to restrict doctors from prescribing Accutane, though legally the FDA had no right to execute the latter. According to physician and co-founder of the Health Research Group, a consumer advocacy organization in Washington, Dr. Sidney Wolfe believed, "What's needed is a departure into restricting who can prescribe the drug and under what conditions, with criminal penalties."[49] In fact, based on the single quote that Altman featured in his article, "The measure falls short of an outright ban," it appears as if he was also advocating stricter restrictions, or essentially, a ban of the drug. For Altman, the FDA's "extraordinary measure" of requiring Hoffmann-La Roche to place a photograph of a deformed child in the warning label, to

[47] Altman, "U.S. Orders Curbs."
[48] Ibid.
[49] Altman, "U.S. Orders Curbs."

sign a consent form with their patients, and so on, was insufficient.[50] On the contrary, despite the evidence clearly suggesting that Accutane is harmful and should be severely limited, many dermatologists said that Accutane is the only treatment available for people who have severe disfiguring acne.

What is interesting to note is the parallel between the Accutane case and the controversy surrounding tobacco regulation in the 1960s: FDA restrictions and evidence of detrimental health effects alone were not enough to discourage consumers from purchasing Accutane and tobacco. In his book *The Cigarette Century,* historian Allan Brandt discusses the lack of any major impact the package labels had on tobacco sales. When it became evident that smoking tobacco was detrimental to the smoker's health, the need for warning labels arose. The Federal Cigarette Labeling and Advertising Act of 1965 required that all cigarette packages include the label, "Caution: Cigarette Smoking May Be Hazardous to Your Health."[51] However, the Federal Trade Commission (FTC) found "virtually no evidence that the warning statement on cigarette packages […] had any significant effect."[52] However, despite the label's wording being modified by Congress twice, the FTC's ban on broadcast advertising, and the FTC's requirement of a warning label on all advertisement in 1972, "cigarette sales and profits remained impressively robust."[53] At this point, given that every cigarette package had a warning label, and thus, smokers were informed of the harms of smoking, tobacco companies could argue that smoking was a *voluntary* risk.[54] However, this argument was weakened by the new anticigarette

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[50] Ibid.
[51] Allan Brandt, *The Cigarette Century: The Rise, Fall, and Deadly Persistence of the Product that Defined America* (New York: Basic Books, 2007), 256.
[52] Olivier Zunz, *Making America Corporate, 1870-1920* (Chicago: University of Chicago Press 1990).
[53] Brandt, *The Cigarette Century,* 258, 273, and 280.
[54] Brandt, *The Cigarette Century,* 323.

movement's recognition of the "innocent victim" (of secondhand smoke).[55] The "innocent victims" were generally nonsmoking women married to smokers or children of smoking mothers whose exposure to cigarette smoke, an environmental toxin, could severely harm them.[56] This notion of the "innocent victim" bolstered the social responsibility side of the argument and shattered the individual responsibility side, which essentially said, "since the risks incurred were entirely to the individual, the authority to regulate and restrict smoking should rest there too."[57] The risks incurred were in fact *not* entirely to the individual; smoking imposes risks on non-smokers too. Brandt explains the irony of this fact: "the impact of smoking on non-smokers, rather than on smokers themselves, is what finally transformed the regulation and cultural perception of the cigarette."[58] Similarly, FDA restrictions and warning labels were not enough to deter the consumer population from purchasing Accutane in the 1980s. However, unlike the tobacco controversy, which considered the dilemma between individual and social responsibility later in its process of administering warning labels, the Accutane case had already deemed the issue of the drug's teratogenic effect to be a matter of social responsibility when warnings against its use by pregnant women were issued the moment Accutane was licensed in 1982.[59] Furthermore, whereas for tobacco, the impact of smoking on non-smokers is what changed the regulation and cultural perception of the cigarette, for Accutane, the teratogenic effect of the drug was not enough to "prevent misuse of Accutane by doctors and patients."[60] Thus, controlling the use of Accutane would require restrictions and measures beyond the inclusion of warning labels. Therefore, while tobacco and Accutane were similar in that warning labels and

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[55] Brandt, *The Cigarette Century,* 281.
[56] Brandt, *The Cigarette Century,* 282
[57] Brandt, *The Cigarette Century,* 281.
[58] Brandt, *The Cigarette Century,* 282.
[59] Altman, "Medical Dilemma."
[60] Ibid.

other regulations were not enough to deter their use, the two cases had major differences that led to different possibilities and opportunities.

Thus, returning to the discussion on the contrasting recommendations for the FDA's next move, the FDA decided that a compromise was the best solution and explained that "further restrictions and unprecedented labeling warnings" would lead to the appropriate use of Accutane, and as a result, there would be no more birth defects caused by use of the drug by pregnant women.[61] Some of the "further restrictions" include: a patient consent form with information on the potential for birth defects, which both the woman and doctor have to sign; the requirement that Accutane should only be prescribed by physicians with special competence in the diagnosis and treatment of severe acne, and who understand the risk of birth defects, i.e. dermatologists; and "extensive professional education and follow-up efforts" by Hoffman-La Roche Inc.[62] Some of the "unprecedented labeling warnings" include: "a drawing of a baby with the syndrome of deformities," in patient information labeling, which would serve as an attention-grabber and a deterrent to women who might not take the warning seriously otherwise; the statistic that "there is at least a ¼ chance that a woman who becomes pregnant while taking Accutane will give birth to a deformed baby;" and the "Don't use in pregnancy" symbol on each page of the patient leaflet and each panel of the new blister-pack packaging.[63] Given the earlier claim made in the CRS Report and the previous discussion on the effectiveness of labels in deterring consumers from purchasing tobacco and Accutane, regardless of how "unprecedented" the labeling warnings are, their potential to minimize Accutane's risks among the female population does not seem as great as Judith Willis expresses. Willis claims:

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[61] Willis, "New Warning," 28.
[62] Willis, "New Warning," 28-29.
[63] Willis, "New Warning," 29.

> This program is a bold example of what can be accomplished when a manufacturer, professional organizations, and FDA cooperate in finding ways to minimize the risks of a drug while preserving its availability to those who can greatly benefit from it. Only time will tell whether the responsible use of Accutane will make the decision to keep it on the market with increased warnings and restrictions […]

Furthermore, since Willis is a member of FDA's public affairs staff and the editor of the FDA Drug Bulletin, her desire to elevate the FDA's role as a powerful agency capable of serving both the pharmaceutical companies and the consumers may skew her assessment of the sufficiency of the proposed restrictions and labels. Perhaps the "further restrictions" have greater potential to both minimize the risks and preserve its availability; however, as seen in the case of tobacco regulation, the effectiveness of labels has less so to do with the features and qualities of the label (i.e. increasing font size, including drawings, stating a statistic), and more so to do with strategically matching the label's content to societal attitudes and priorities at the right time.

Ethical Dilemma

The case of Accutane presents a very important ethical question: should a drug that has potent ability to treat a disfiguring form of acne be taken off the market because if taken by a pregnant woman, it is very likely to cause malformations in her baby or even result in a miscarriage. In her article published in the *FDA Consumer* in 1988*,* Judith Willis identifies four main issues:

1) "Accutane was known to cause birth defects in animals and suspected of causing them in humans even before it was approved by FDA in 1983." In addition, despite the drug's label, which read that use of Accutane was forbidden during pregnancy, it was still used.
2) Although the severe form of acne, called severe recalcitrant cystic acne, which Accutane could treat, was much more common in males than in females, 40% of the

prescriptions were written for women of childbearing age; women simply sought treatment more often than men.

3) Accutane was the only drug available to clear severe recalcitrant cystic acne – it was extremely potent.
4) There were repeated revisions of the labeling and strong recommendations that the drug should not be used by women of childbearing age unless they were using an effective form of contraception; however, the numbers of birth defects and miscarriages continued to increase.

Considering these issues, the Centers for Disease Control (CDC) and the American Academy of Pediatrics (AAP) on one hand advised the FDA to withdraw Accutane from the market; while on the other hand, the American Academy of Dermatology (AAD) (dermatologists wrote 90% of all Accutane prescriptions) recommended continuing to market the drug but with a number of restrictions.[64] In fact, at a Dermatologic Drugs Advisory Committee meeting in April 1988, representatives from the FDA, CDC, AAP, and AAD convened to discuss solutions in an effort to address the four issues. While the CDC and AAP included photos of babies with misshapen heads, lack of ears, and cleft palates, in their presentation to persuade the FDA to withdraw Accutane, the AAD showed photos of patients with severe recalcitrant cystic acne and highlighted Accutane's "therapeutic value and the physical and psychological scarring, along with the social ostracism," that patients endure.[65] Such photos and testimonies were actually quite commonly published in newspapers during both the thalidomide and Accutane incidents. For example, Jamie Swenholt's story was shared in the *Washington Post*:

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[64] Judith Willis, "New Warning About Accutane and Birth Defects," *FDA Consumer,* October 1988, accessed October 12, 2016.
[65] Willis, "New Warning," 27.

> Jamie was a thalidomide child who was "born with malformations of all four limbs, mental retardation and other handicaps." "Her head was abnormally small and misshapen. Her arms were deformed and shortened… One leg was very short, with a club foot, and extra and webbed toes. The other, also very short, was permanently bent behind and to the left of her thigh; later, the lower portion of the leg was amputated, in in one of a series of operations. There were anomalies of the eyes, ears, nose, nose, hips, wrists, elbows, knees, and bone structure. In childhood exams, she was found to be hard of hearing, to have a vision problem, to have no tear ducts, and her father says, to have a potential mental development that 'will never go beyond age 9.'"[66]
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> See Figure 2: a photo of Jamie Swenholt.[67]

An example of a personal experience regarding the use of Accutane is Carla Jenner and her daughter's story, published in the *New York Times:* "The infant girl had hydrocephalus, or water on the brain… Her face and ears were malformed, and she had severe brain abnormalities. The baby, now over a year old, is profoundly retarded and is kept alive through round-the-clock nursing at a chronic care facility."[68] It is interesting to note, however, that none of the newspaper articles that this paper analyzed included any personal testimonies on individuals who directly shared that thalidomide and Accutane were indeed "miracle" drugs. It is very likely that there were men and non-pregnant women who would have genuinely spoken highly of these drugs' potent treatment effects; however, these individuals may have felt uncomfortable sharing so, given that the drugs were also causing physical deformities in babies, or the journalists wanted to share a particular story with a specific message, such as one that criticized the FDA's lack of initiative and action in protecting the health of the drugs' consumers. By including personal testimonies and extremely descriptive language, these journalists were expressing their opinions on the ethical questions at stake regarding efficacy, profits, and sales vs. safety of the consumers.

Conclusion

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[66] Mintz, "She's 19, Deformed."
[67] Ibid.
[68] Blakeslee, "Drug That Often Cures."

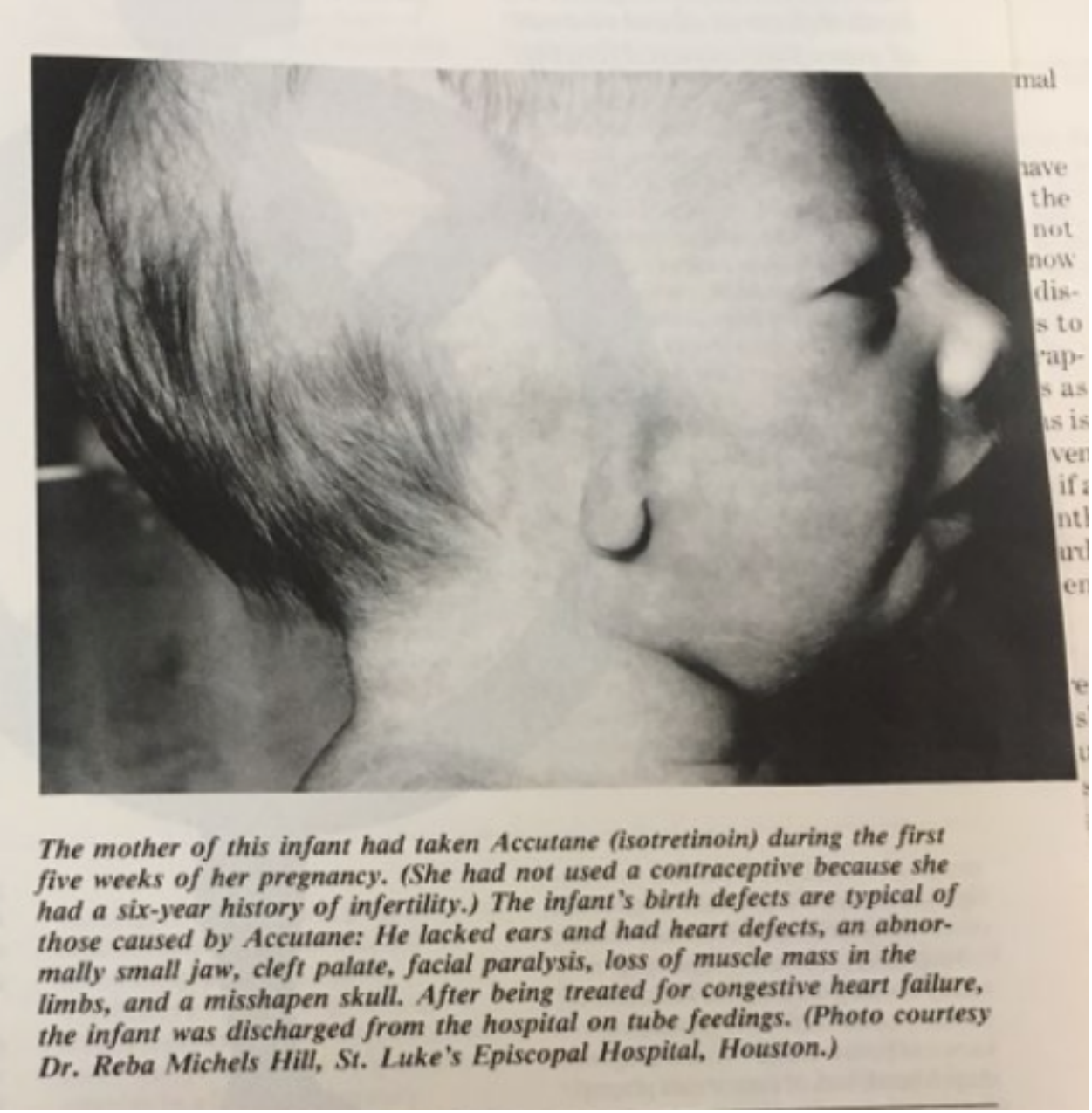
Given the history of the thalidomide incident in the U.S. – the relatively weak impact the drug had on the U.S. population; the heavy media coverage of Dr. Frances Kelsey, thalidomide babies, and the FDA; and the passing of the Kefauver-Harris Amendment – one may think that the Accutane tragedy should and could have been avoided. Thus, in an attempt to find out what Accutane's story was and retell it in the context of the history of pharmaceutical regulation, I read and analyze news articles written throughout the second half 20th century. These news articles were not just compilations of facts, events, and individuals of the time; they were actual stories told by people experiencing and witnessing the controversies occurring right before their eyes. Thus, given the various backgrounds and perspectives these journalists had to offer, though their stories were all on the thalidomide and Accutane cases, they all told different stories. Therefore, this paper attempted to piece these stories together along with FDA primary source materials and secondary sources, in order to construct and tell a completely new story of the same two incidents.

Journalists living during thalidomide controversy attributed its happy ending to Dr. Frances Kelsey, who indeed played a significant role but not the only role. What the stories in the news articles do not include is the role played by Congress, who organized and set the stage for Dr. Kelsey to be the 'heroine' of the story. However, the greater political agenda that was behind this carefully orchestrated media exposure was to garner public support for more drug regulations and power for the FDA. Congress and the FDA successfully achieved their goal as shown by the passing of the Kefauver-Harris Amendment in 1962. This hidden political agenda embedded in Dr. Kelsey's rise to fame was absent in all the news coverage that I had analyzed. Furthermore, the fact that the Kefauver-Harris Amendment was passed in order to grant the FDA more powers, combined with the journalists' criticisms of the FDA's weak restrictions, the CRS

Report's statement on the questionable effectiveness of labels, and the history of U.S. tobacco regulations, presents an extremely ironic storyline. Given that one of the major components of the Kefauver-Harris Amendment was drug safety, and it was a product of the thalidomide incident, one would expect that Accutane would not have had as severe of an impact on the U.S. as it did. That was the very mystery of Accutane.

Close analysis of the news articles revealed the journalists' concerns that the FDA restrictions on Accutane use were not stringent enough. However, the journalists did not address why these regulations appeared ineffective and not sufficient for controlling the use of Accutane by pregnant women. On the other hand, the CRS Report and the analysis of the use of labels in tobacco regulation *did* address why the FDA regulations on Accutane seemed to have no effect. Thus, by synthesizing the stories told by journalists, the sources by various players in both our national and international governments, and the cases of other drugs regulated by the FDA, this paper constructed and told a completely new story.

Thus, the cliché answer to why history is important is not so cliché after all. Though it may appear that we repeat the same mistakes over and over again throughout history, as seen in the case of Accutane, there are so many circumstances, actors, and intentions that are not even mentioned in the stories that are written in the past. One report may be biased, some journalist may have only had access to half of the story, and perhaps a new regulation was intended to serve purpose X, but was practiced in a way that served purpose Y. Therefore, history is indeed important because we want to avoid going down the same wrong paths that we have in the past, and in order to do so, we must constantly attempt to debunk the mysteries that surround us.



The mother of this infant had taken Accutane (isotretinoin) during the first five weeks of her pregnancy. (She had not used a contraceptive because she had a six-year history of infertility.) The infant's birth defects are typical of those caused by Accutane: He lacked ears and had heart defects, an abnormally small jaw, cleft palate, facial paralysis, loss of muscle mass in the limbs, and a misshapen skull. After being treated for congestive heart failure, the infant was discharged from the hospital on tube feedings. (Photo courtesy Dr. Reba Michels Hill, St. Luke's Episcopal Hospital, Houston.)

Figure 1.

By John McDonnell — The Washington Post

Jamie Swenholt and parents: The pills Donald Swenholt took home from an Alabama military hospital when his wife, Frances, was pregnant are still haunting them.

Figure 2.

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