Identifying social factors that influence sex-specific policy in the regulation of clinical trials

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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Introduction

Perhaps the most important part of a medicine's journey to approval is the clinical trial phase of research. The Food and Drug Administration (FDA) defines clinical trials as "…voluntary human research studies designed to answer specific questions about the safety and effectiveness of drugs, vaccines, devices and other therapies…". While organizations attempting to release their treatment to the market are responsible for conducting clinical trials, the FDA is the governing body that sets clinical trial regulations and evaluates the data from trials to approve or reject the treatment ("FDA Encourages More Participation…", 2018). Data gathered from these studies are aimed at elucidating the safety and efficacy of drugs before they are released to market for use by patients. In order for an emerging therapeutic to be approved by the FDA, it not only has to be safe and efficacious but also has to be more effective than or produce less harm to patients than the current standard of care.

With clinical trials being such a critical step in a drug's road to market, ensuring that the practices used to regulate them will produce accurate and meaningful results on a population representative of the patient population that will use them is key to user safety; however, this has not always been the case. The FDA has had a history of excluding females from clinical trials with the peak of this exclusionary activity being in 1977 with the passage of the guideline "General considerations for the clinical evaluation of drugs". This guideline suggested that all premenopausal women that could become pregnant be excluded from phase I and phase II clinical trials (Liu & DiPietro Mager, 2016). Biological differences existing between males and females has the potential to affect the ways in which drugs are absorbed and modify the function of the body. This means exclusion of females from clinical trials could result in unexpected

adverse drug effects once medicines are released to market that failed to be uncovered during the clinical trial period.

In this analysis, significant historical events that formed and shaped the FDA will be introduced to provide context as to how and why the FDA regulates the pharmaceutical market. Then policies that included sex-specific regulation of clinical trials will be introduced along with two cases in which lack of female representation in clinical trials resulted in unexpected market outcomes. The analysis will look to perform a study of the social factors influencing women's inclusion or exclusion from drug clinical trials and the level of evaluation of sex-dependent data will be conducted along with their implications.

Social construction of technology (SCOT) as a framework for analyzing social factors influencing clinical trial regulation

In analyzing the social factors that influence the exclusion of people from clinical trials based upon sex, the social construction of technology (SCOT) framework will be used. This framework states that society plays a key role in shaping technology rather than the reverse posited by the technological determinism framework in which it is believed that technology shapes society. SCOT identifies key stages of a technology's usefulness in society including interpretive flexibility and closure. Interpretive flexibility acknowledges the ways in which design flexibility as well as a technology's perceptions can change depending on the social group examining the technology. These different interpretations of technology can lead to conflicts regarding the technology as relevant groups may have competing views on the ways in which a technology should be implemented in society. As technologies continue to be developed according to societal needs, they will eventually reach the phase of closure in which conflicts surrounding the technology are resolved through design or reframing of the problems

surrounding the technology. If a technology fails to meet the needs of society through closure, it will eventually be deemed not useful and be phased out of use.

SCOT is well-suited for the analysis of the social factors shaping sex-based exclusion from clinical trials as it accounts for the ways in which changing social views along with elevation of different relevant social groups impacts trial regulations. Throughout the analysis, clinical trials will be considered the technology in question and the ways in which societal views at the time influenced legislation surrounding the evolution of clinical trials will be examined. Relevant social groups are the FDA and the United States government, pharmaceutical companies looking to release drugs to market, clinical trial participants, and users of approved medications once they reach the market with an emphasis on women. Through the lens of these social groups, the ways in which FDA regulations had to use design flexibility to evolve in a way that kept the clinical trial a relevant and useful technology capable of accomplishing the need it sets out to meet will be elucidated.

Historical context of the FDA's role in clinical trial regulation

With advances in medicine and medical practices in the early twentieth century, society began recognizing a need for well-controlled studies of medicine and the way it modifies the body's function. At the time, categorization of a study as "well-controlled" recognized the need for both laboratory studies on medications followed by human studies to evaluate safety. The societal need for a standardized mechanism through which emerging therapeutics could be studied before becoming widely available led to the passing of the U.S. Food, Drug, and Cosmetic Act in 1938 which subjected new drugs to pre-market safety evaluations. While this act did not specify the tests and kind of data that would need to be acquired for the FDA to approve a drug, it was a turning point in regulatory requirements of pharmaceutical agents in that

the FDA was required to review pre-clinical data from the lab and clinical data from human trials and they had the authority to halt release of a drug to market should more data need to be acquired to prove a drug's safety (White Junod, 2016).

The relatively ill-defined role of the FDA and clinical trials become much stricter following a large-scale drug-related medical disaster in 1961. The drug thalidomide, prescribed to treat morning sickness in pregnant women, resulted in the birth of over 10,000 children with malformities ranging from severe to completely debilitating. Originally released in the 1950s by a German pharmaceutical company, this drug was marketed as a safe alternative to anti-emetics commonly prescribed at the time. It wasn't until two independent clinicians confirmed the link between rising birth defects to thalidomide that it was banned from markets in 1961. Notably, although this drug was available in nearly every major market in the world at the time, FDA researcher Dr. Frances Kelsey barred its marketing in the United States due to safety concerns. Nonetheless, this tragedy altered the regulation of drugs with human clinical trials becoming a requirement for a drug to be released to market (Vargesson, 2015).

Following the thalidomide disaster, the US government signed into effect the 1962 Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act of 1938. These amendments laid the groundwork for today's phased clinical trial system as well as the necessity for pre-clinical data to prove the safety of testing a new drug on human participants (Greene & Podolsky, 2012). According to the Kefauver-Harris Amendments, manufacturers had to prove efficacy of treatments, not just safety, before release to the market. The act also requires reporting of any serious side effects once the drug is on the market, regular inspection of manufacturing facilities to ensure good manufacturing practices (GMPs), and allowed the FDA to control advertising of drugs (*Kefauver-Harris amendments…*, 2012).

The path to approval: today's clinical trial process

Before entering the clinical trial phase, a drug must go through the preclinical process in which basic questions about a drugs safety are answered. These tests are conducted in the lab and on animals. Once this data is collected and submitted to the FDA, entities looking to manufacture and market a therapeutic agent must submit a detailed plan about how the clinical trial for that treatment will be run. This plan must answer several key questions including who qualifies as a participant in the trial, how many people will be in the study and for how long, how the drug will be given to patients and at what dosage, and how data will be collected and analyzed. All of the preclinical information gathered on the drug as well as the clinical trial plan are submitted to the FDA in one package known as an investigational new drug application (IND). Once the IND is approved, manufacturers can move into the phased portion of the clinical trial process where human subjects first become involved.

There are four stages to the clinical trial process each serving their own purpose. Phase I involves a small number of healthy participants that take the drug for several months to confirm its safety and find the appropriate dosage. Phase II will have several hundred participants with the disease or condition the drug is aiming to treat and lasts several months up to two years. The purpose of this phase is to determine the drug's efficacy and any side effects that may result from its use. Phases III and IV will have anywhere from a few hundred to a few thousand patients with the condition the drug is meant to treat and last for several years in order to determine efficacy and monitor for any long-term effects that can result from taking the drug over an extended period of time. Table 1 summarizes these phases along with the success rate of drugs in each phase.

Phase	Purpose	Number of Participants	Length	Percent of drugs that move to the next phase
1	Safety and dosage	20-100 healthy or diseased participants	Several months	70%
2	Efficacy and short-term side effects	Up to several hundred patients with disease	Several months to 2 years	33%
3	Efficacy and monitoring of adverse reactions	300-3,000 patients with disease	1-4 years	25-30%
4	Safety and efficacy	Several thousand patients with disease	1-4 years	N/A

Table 1: FDA clinical trial phases along with their purpose, requirements for participants and length, and success rate. Only about 10% of drugs that begin the clinical trial process make it to market.

Throughout the process, the FDA or manufacturer can choose to end the trial and pull the drug from consideration for approval if data is showing that the drug is not safe or efficacious. If the drug meets the FDA's requirements through each phase and proves to be more efficacious or produce less harmful side effects than the current standard of care, the manufacturer will submit a marketing application to be approved or denied by the FDA (*Step 3: Clinical research,* 2018).

FDA releases sex-specific policies

When evaluating the key turning points in the formation of the FDA and the transformation into the governing body it is today, one can see the ways in which society shaped the clinical trial process. For example, the passing of the Kefauver-Harris Amendments arose after birth defects which were not seen in animal trials resulted from widespread thalidomide use in pregnant women. With this event, two social groups emerged as dominant forces in the need for an evolution in the clinical trial process: the FDA and the drug consumer. In correcting the lack of restrictions in place for a drug to reach the market, society took drastic measures and greatly increased the power of the FDA to regulate such processes.

Arguably, the ability for the FDA to assert regulatory control over the manufacture of drugs led to a safer and more standardized practice that protected consumers; however, the

newfound appreciation for how dangerous medicines could be led to the exclusion of a key demographic from the early phases of clinical trials. Following the thalidomide tragedy, the FDA wanted to minimize the odds of such future events happening and in a move that could be considered somewhat contradictory to this goal published the 1977 guideline General Considerations for the Clinical Evaluation of Drugs. This set of guidelines is notable for its section titled "Women of Childbearing Potential":

> A woman of childbearing potential is defined as a premenopausal female capable of becoming pregnant. This includes women on oral, injectable, or mechanical contraception; women who are single; women whose husbands have been vasectomized or whose husbands have received or are utilizing mechanical contraceptive devices…
>
> In general, women of childbearing potential should be excluded from the earliest dose ranging studies.

This document essentially excludes all premenopausal women capable of becoming pregnant from participating in phase I and early phase II clinical trials—the parts of the trial meant to establish the safety and dosing information of drugs.

Examining this guideline using the SCOT framework, relevant social groups can be seen as the FDA and consumers of drugs. In order to assert the importance of clinical trials as a means to ensure the safety of the public both during trials and after release to the market, the FDA saw it as necessary to ensure replication of the thalidomide disaster did not occur. It was important for the clinical trial to be deemed as effective in increasing patient safety for society to justify the need for such strict regulation of commercial products as this had not been seen before.

Additionally, a repeat of the birth defects seen with thalidomide would create public mistrust in clinical trials, risking its descent into an irrelevant technology.

Though the FDA was looking to avoid risking the health of patients in the clinical trial process by excluding all women of childbearing potential, it could be argued that the organization was threatening rather increasing patient safety with this act. Phases I and II of clinical trials are meant to establish important information about safety and dosing of drugs. By excluding all premenopausal women from these studies, the administration is missing key information as to how emerging therapeutics will be metabolized and change the function of the bodies of females within this age category. Furthermore, imposing such restrictions removes the agency of women to select whether they wished to participate in a clinical trial even when informed of all of the possible risks associated with it.

As expected with the publication of General Considerations for the Evaluation of Drugs, women were severely underrepresented in clinical trials with the peak of this inequality taking place in the late 1970s and 1980s. Examples illustrating this inequality include the Physicians' Health Study of the effects of aspirin on cardiovascular disease in which 22,071 males were enrolled compared to 0 females and the Multiple Risk Factor Intervention Trial (1973-1982) in which 12,866 males were enrolled compared to 0 women (Schiebinger, 2003). With the emergence of the women's health movement as part of the women's movement in the throughout the 1980s, clinical trials had to once again had to utilize design flexibility in order to remain a relevant technology in the eyes of society; however, with this iteration of clinical trials women emerged as their own relevant social group.

Advocacy for equal representation of the sexes in clinical trials resulted in the 1993 publication of Guidelines for the Study and Evaluation of Gender Differences in the Clinical

Evaluation of Drugs. This guidance essentially reversed the FDA's 1977 publication including information about how the restriction against participation of women capable of becoming pregnant has led to a paucity of female participation as a whole. According to the 1993 publication:

> The patients included in clinical studies should, in general, reflect the population that will receive the drug when it is marketed. For most drugs, therefore, representatives of both genders should be included in clinical trials in numbers adequate to allow detection of clinically significant gender-related differences in drug response.

The document also encourages those running clinical trials to look for data discrepancies between the sexes that could be attributed to sex-related pharmacokinetic differences in the metabolism of drugs. With the rise of the women's health movement, women were able to establish themselves as their own relevant social group apart from the rest of drug consumers. This emergence of a new prominent social group led to the adaptation of clinical trials into a technology that was useful for a wider group of people as to avoid failure in accomplishing its task of making drug consumption safe once medications reach the market. Through iterative mechanisms that satisfied social groups dominating the conversation around clinical trials and health at the time, clinical trials were able to stabilize and remain a relevant technology.

This publication was key for ensuring that both sexes were represented in clinical trials; however, many drugs were approved for use based off of clinical trials that had disproportionate male participation. Such drugs had their dosing and critical safety information determined largely without female participation, greatly impacting the pharmaceutical industry even decades later. Two cases in which drugs had drastically different effects on males and females will be

examined to glean insight into how the FDA's 1977 General Considerations for the Clinical Evaluation of Drugs has had a lasting impact on the pharmaceutical industry.

Case 1: Digoxin in the 1990s

Digoxin is a medication prescribed to treat heart failure and abnormal heartrates (arrhythmias) through neuromodulatory mechanisms (Steckelberg & Newman, 2010). Many of the trials to approve digoxin were carried out through the late 1970s and 1980s and as such had a disproportionate number of men enrolled than women in these trials. When there appeared to be an unexpectedly high rate of mortality of patients that were prescribed digoxin to treat heart failure or arrhythmia, the Digitalis Investigation Group conducted a study on the medication's effects in 1997. The group reported that digoxin did not reduce overall mortality from heart abnormalities for patients prescribed the medication but it did reduce hospitalizations both overall and for worsening heart failure (The Digitalis Investigation Group, 1997).

As a result of the findings of this study, the American College of Cardiology and the American Heart Association strongly endorsed digoxin as a treatment for patients experiencing arrhythmia or who had an incident of heart failure. In a post-hoc analysis of the data collected from The Digitalis Investigation Group's 1997 study, Rathore, Wang, and Krumholz found that digoxin in fact did increase patient mortality, specifically in women. The authors noted that "though epidemiological features, causes, and prognosis of heart failure vary between men and women, sex-based differences in the effect of digoxin were not evaluated" (Rathore, Wang, & Krumholz, 2002). Through the post-hoc data analysis, it was found that there was an absolute difference of 5.8% between men and women in the effect of death rate. Furthermore, women had lower digoxin-related reduction in repeat hospitalization for cardiac events. Not only is this medication less effective for women than men but it is also more dangerous for women to

receive this treatment. Though no definitive cause for the discrepancy of treatment results with digoxin could be uncovered, it was suggested that it may be due to differences in the pharmacokinetic action of the drug in women as there were higher amounts of residual digoxin found in blood draws from female participants (Rathore, Wang, & Krumholz, 2002).

Failure to recognize the sex-based differences in the actions of digoxin are an artifact of the exclusion of women from clinical trials throughout much of the 20th century and a failure to analyze sex-specific outcomes of drugs. Though the initial 1997 study was conducted after the FDA revised its gender-specific guidelines, there was still a failure by the Digitalis Investigation Group to examine the ways in which the drug may be affecting male and female participants. As such, a drug that is more dangerous for women to take and less effective in its curative capacity was endorsed by leading institutions for cardiac health. This failure by clinical trials to serve the needs of all relevant social groups even after reparative action was taken by the FDA to improve its technology demonstrates the importance of considering all relevant social groups in the earliest stages of technological development.

Case 2: Zolpidem in the 1990s

Zolpidem is a non-benzodiazepine sedative that was widely marketed as a treatment for insomnia with initial release to the US market in 1993 (Kirkwood, Neill, & Breden, 2007). After its release to market, women were reporting drowsiness and trouble driving the morning after they took zolpidem for insomnia. Further evaluations of 14 studies showed that women appeared to be more impaired in driving after taking zolpidem the night before. When evaluating causes for this, it was found that there are pharmacokinetic differences in the way the drug is cleared between males and females resulting in a higher residual level of zolpidem for females even 4 to 5 hours after waking up in the morning (Chu, 2014).

As a result of the repeated findings that females had higher residual amounts of zolpidem and therefore at risk for increased drowsiness the following day, the FDA recommended cutting the dosage of the drug by 50% for women in 2014. This only occurred after a decade of marketing the drug without any warnings as to how a female receiving the recommended dose for a male could cause cognitive impairment (Zucker & Pendergast, 2020; Liu & DiPietro Mager, 2016).

Here, the lack of inclusion of all relevant social groups in the initial construction of clinical trials is evident. Due to the lack of representation by females and further failure to analyze the ways in which drugs impact the sexes differently, a medication that should have been prescribed in half of its current dose was marketed for ten years in a form harmful to females. Though women were able to establish themselves as a relevant social group in the healthcare field specifically as critical stakeholders in the clinical trial process, there are still implications from a time in which they were left out of trials. Even today, there e sex-specific effects of drugs are understudied though it has been proven that inherit biological differences between males and females affect a medication's pharmacokinetics.

Conclusion

This analysis examined the ways in which social factors influenced sex-specific policies regulating clinical trials. Though clinical trials regulated by the FDA have emerged as the mandatory means through which drugs are deemed safe and efficacious for market in the US, they have not always and arguably still are not protecting all consumer. Women emerging as a relevant social group apart from the rest of the drug consumer market played a major role in ensuring that regulations surrounding clinical trials became representative of populations taking medication. Even still, there is a lack of analysis on the sex-specific effects of drugs being

released to market raising important safety concerns as shown by the cases of zolpidem and digoxin. Studies performed to elucidate discrepancies in underlying mechanisms that impact the ways in which medication alter bodily function demonstrate the importance of ensuring that clinical trials represent the patient population they are meant to serve. Through design flexibility, clinical trials have been able to remain a relevant technology and reach stabilization through multiple conflicts; however, the lasting impacts of exclusionary language being built into foundational regulations demonstrate a need for clinical trials to mandate that all relevant social groups are included when approving or denying a medication's release to market.

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